

Evidence Based Dermatology

Second Edition

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Albert & Lorraine Kligman

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Preface

This book is for practitioners at any stage of their career who have clinical, teaching, or research interests in the management of cutaneous diseases. It is critical to attempt to manage patients based on evidence based principles; however, it is even more important to remember that relying on the best evidence is not the only factor in delivering the best care for each patient. Patients' beliefs and preferences should also be considered. This is why the individual patient is the central focus of evidence based decision making. Physicians are not only dealing with facts and odds (e.g. handling a computerized stock market trading system) but also a human being with feelings, intelligence, judgment, fears, preferences, and values. Having said that, we believe this book will be more useful for patients if the physician applies the recommendations in the light of the patient's conditions and healthcare provider's competencies. Additionally, the hierarchy of evidence is always important. This basically means that even though systematic reviews and randomized controlled trials are the best available resources, it is not enough to limit your analyses to the best evidence. In a recent study, Golder et al. performed a comprehensive meta-analysis to assess the level of agreement or disagreement in the estimates of harm derived from meta-analysis of RCTs as compared to meta-analysis of observational studies. They noted that observational research can be as credible as randomized trials when investigating side effects of a drug. It is also essential to utilize the major models to report different types of studies such as CONSORT for randomized controlled trials, PRISMA (formerly QUOROM) for systematic reviews and meta-analyses, STROBE for observational studies and STARD for diagnostic studies. These guidelines were not created to impose rigid structural disciplines. They only require the authors to include all of the items from a checklist properly and explicitly anywhere in the manuscript. We suggest that our readers use these tools to interpret any published report or to design and report their own projects. "Evidence based medicine" is a growing phenomenon; however, it has not been fully integrated into medical education in the field of dermatology. We encourage all dermatology faculty members specifically dermatо-epidemiology experts to

develop a well defined explicit strategy to integrate EBM better into their residency/clerkship training programs.

In this second edition, we have reduced the content of the chapters on "principles of evidence based medicine", as we assume many of those principles have been engraved in the minds of our readers. Additionally, we avoid using detailed epidemiological language unless it is necessary to convey a specific concept. Thus, you will find a small number of introductory chapters in parts of this book. We have introduced new sections including a section entitled "Diagnosis of a cutaneous disease," where diagnostic evidence in dermatology is briefly reviewed. Studies on risk factor analysis for cutaneous diseases are also reviewed in a new section. Furthermore, specific modalities were examined in order to obtain more detailed evidence based details on efficacy and safety. At last but not least, cost effectiveness studies are another new focus in this book. We do not attempt to review all dermatological diseases in this book but rather bring up new horizons in evidence based dermatology. Our mission is to introduce and encourage the use of different evidence-based strategies among our readers in their daily practice and, if applicable, in their teaching/education. Please remember that evidence based learning is a lifelong process not a two day workshop.

We are honored to be a part of a legendary team of 140 outstanding contributors from the States and 14 other countries.

We would also like to thank Mr. Martin Wonsiewicz, President of PMPH-USA, Mr. Jason Malley, Executive Editor, Ms. Shirley Blum, Executive Assistant – Editorial, and Ms. Surinder Sharma, Production Manager, for their extraordinary and visionary insight, full support and hard work.

The editors strongly encourage the readers to comment on the contents of the book and inform them of any corrections. They will be acknowledged in the next edition. We also welcome any general recommendations to help improve the next edition.

Howard I. Maibach, M.D.
Farzam Gorouhi, M.D.
May 2011

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Diagnosis



Studies and Systematic Reviews on Diagnostic Test Accuracy

Alireza Khatami, M.D., M.S.P.H., and Farzam Gorouhi, M.D.

*"A smart mother makes often a better diagnosis than a poor doctor"**

August Karl Gustav Bier (1861–1949)¹

INTRODUCTION

Diagnostic tests are a group of interventions that are used for differentiation between individuals who do or do not have a particular condition, such as a disease. The optimal goal of a diagnostic test is to identify those who will benefit from certain therapeutic or preventive interventions and to determine the prognosis of the condition.^{2,3} Figure 1-1 shows the correlation between test threshold, intervention threshold, and the proper situation for using a diagnostic test.

David Sackett, the father of modern evidence-based medicine (EBM), defined this as "the conscientious, explicit, and judicious use of current best evidence in making clinical decisions regarding the care of individual patients."⁴ This definition implies that EBM should answer all clinical questions about the diagnosis, prevention, treatment, and prognosis of a disease. Unfortunately, in the earlier years of the development of EBM, it mostly focused on therapeutic interventions. Dr. Gordon Guyatt and his colleagues at McMaster University started to establish a more explicit methodology for EBM around two decades ago.⁵ This trend has since been extensive and ever changing. However, many physicians and academicians still have limited competency

BOX 1-1—Abbreviations that are Commonly Used in this Chapter

DOR:	Diagnostic odds ratio
EBM:	Evidence-based medicine
+LR:	Positive likelihood ratio
-LR:	Negative likelihood ratio
NPV:	Negative predictive value
PPV:	Positive predictive value
QUADAS:	Quality Assessment of Diagnostic Accuracy Studies
ROC curve:	Radio operating characteristics curve
SROC curve:	Summary radio operating characteristics curve
STARD:	Standards for Reporting Diagnostic Accuracy

to integrate EBM as a tool in their routine clinical practice, as well as in the area of therapeutic interventions, and dermatologists are no exception.

Because of the wide spectrum of relevant entities in dermatology, a vast spectrum of diagnostic tests are used in this field. For example, several methods can be used in the diagnosis of cutaneous leishmaniasis. These include direct smears, culturing on certain media, histopathologic examination, isoenzyme assay, and the polymerase chain reaction (PCR).^{6–9} Further, different diagnostic methods are used

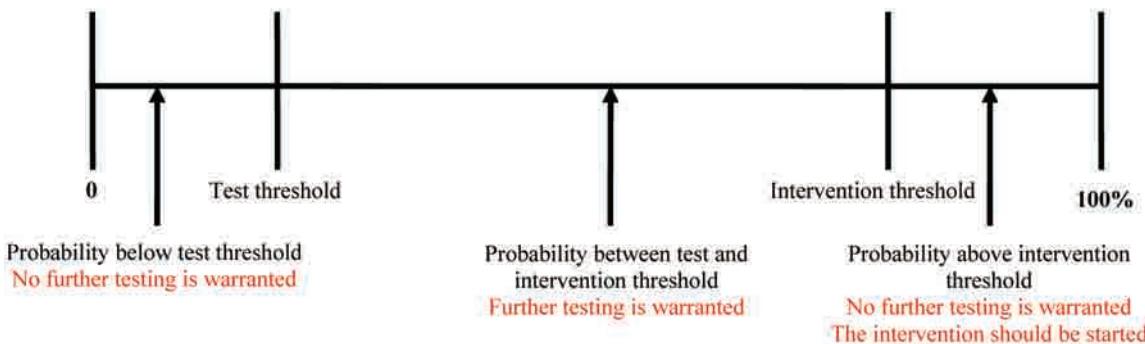


FIGURE 1-1 Proper place for requesting a diagnostic test on the continuum probability of diagnosis for making decision for administration of a certain intervention.

¹ Some quotations always remain memorable just like this quotation by Dr. August Bier (German surgeon, 1861-1949).*

for accurate diagnosis of pigmented skin lesions. Besides routine histopathologic examination, other groups of diagnostic tests, such as immunohistochemistry, dermoscopy, and confocal microscopy, may be used.^{10–12}

Unfortunately, the problem is sometimes more profound. For some cutaneous diseases, such as pemphigus vulgaris, there is no definitive “gold standard” test, and this makes it even more difficult for dermatologists to reach an accurate diagnosis and adopt the optimal approach for a patient. There is no universally accepted single test for pemphigus vulgaris based on worldwide expert opinion surveys.^{13,14} Diagnostic options for pemphigus vulgaris are histopathologic examination of a biopsy specimen, direct and indirect immunofluorescence, a Tzanck smear, and use of the Nikolsky sign. None of these methods, alone or in combination, can provide a completely accurate diagnostic tool for this condition. This part of the problem cannot be immediately solved by EBM; therefore, it is necessary to acknowledge that the problem always exists and that it should be considered.

This brings up a philosophical question: Why do physicians diagnose an abnormal condition? Is this only for determining treatments? The short answer is “no,” because a diagnosis can also enlighten the patient in terms of the details of the disease and its risk factors and prognosis.¹⁵

Let us imagine that a physician is not 100% sure that a patient has any of the following dermatoses: atopic dermatitis, allergic contact dermatitis, irritant contact dermatitis, and drug-induced bullous disorder.

Sometimes an exact diagnosis is not essential to guide therapy because the mainstream treatment of choice (corticosteroids) would be similar for all these diseases. Nonetheless, it is still important to obtain an exact diagnosis. For example, most bullous drug eruptions are resolved once the causal drug is removed. In atopic dermatitis and allergic and irritant contact dermatitis, prevention of acute flares and the subsequent development of chronic lesions are indicators for successful treatment. Therefore, if the possible cause can be narrowed down to a specific contact allergen, the disease can be controlled more efficiently.

The need for accurate tests to aid proper decision making is critical at two important levels: clinical practice and health policymaking. In addition, novel diagnostic technologies support the growing need for a diagnostic evidence-based approach.^{2,16} There is a similar current trend in dermatology.

In this chapter, we briefly review important issues related to the quality of design and reporting in diagnostic studies. These studies can provide raw data for systematic reviews and may provide the highest level of available evidence in the absence of systematic reviews.

STUDIES ON DIAGNOSTIC TEST ACCURACY

It is obvious that diversity is seen among diagnostic tests and related studies. However, the accuracy of a diagnostic

test is the main concern for physicians. We have therefore chosen the diagnostic accuracy of a test as the starting point for further discussions on basic issues in a diagnostic study, as well as those concerning diagnostic systematic reviews. Some recapping information on the main outcomes of this type of study is provided below.

MAJOR OUTCOME MEASURES AND BASIC DEFINITIONS IN DIAGNOSTIC ACCURACY STUDIES

Let us consider that the results of the gold standard and index tests are dichotomous. This is actually an oversimplification for most of these diseases, because both the disease-positive and disease-negative populations may represent a spectrum of responses to testing. For example, different subtypes of cutaneous melanoma have different levels of aggression. Additionally, some melanoma tumors are localized (stages I and II), some are metastasized to sentinel lymph nodes (stage III), and some have distant metastases (stage IV). Conversely, the disease-negative population may consist of patients with any other type of skin cancer or dermatologic condition, or disease-free subjects. Therefore, a dichotomy of this type is not a perfect paradigm, although it is the most acceptable default. A 2-by-2 table is used to define the main outcomes in a diagnostic accuracy test (Table 1-1).

Based on the data in Table 1-1, the definitions of major outcomes are:

- Sensitivity = The proportion of participants with the condition of interest who have a positive test result ($a/a + c$)
- Specificity = The proportion of participants without the condition of interest who have a negative test result ($d/b + d$)

The following mnemonics may be helpful to remember the roles of highly sensitive and highly specific tests in a clinical setting:¹⁷

- a. SnNOUT, which means a negative result of a test, which is highly sensitive for presence of a condition, rules out that condition.

		TABLE 1-1—A 2 by 2 Table	
		Condition of interest	Total
Test result [†]	+	-	
	a	b	$a + b$
-	c	d	$c + d$
Total	$a + c$	$b + d$	$a + b + c + d$

* Presence of condition of interest (+) is based on the result of the gold standard test. [†] Test result reflects result of the index test. a = true positives (TP), b = false positives (FP), c = false negative (FN), d = true negatives (TN), $N = a+b+c+d$.

- b. SpPIN, which means a positive result of a test, which is highly specific for a condition, rules in that condition.
- False positive rate = The proportion of participants without the condition of interest who have a positive test result ($b/b + d$)
 - False negative rate = The proportion of participants with the condition of interest who have a negative test result ($c/a + c$)
 - Positive predictive values (PPV) = The proportion of participants with a positive test result who have the condition of interest ($a/a + b$)
 - Negative predictive value (NPV) = The proportion of participants with a negative test result who do not have the condition of interest ($d/c + d$)
 - Test accuracy = $(TP + TN)/N$ = The proportion of those tested in which the index test gives the correct answer $(a + d)/(a + b + c + d)$
 - Positive likelihood ratio (+LR) = sensitivity/(1-specificity)
 - Negative likelihood ratio (-LR) = (1-sensitivity)/specificity

A test can diagnose the condition of interest accurately if it has a +LR greater than 10. Positive LR values more than 2 and more than 5 are considered as clinically useful and clinically very useful, respectively. A test can rule out a condition correctly, if it has a -LR less than 0.1.¹⁷

- Pre-test probability = The prevalence of the condition of interest
- Post-test probability = The probability of the condition of interest after using a likelihood ratio (LR) nomogram, which works as a graphical calculator based on Bayes' theorem (Figure 1-2).^{1,2}
- Odds (pre-test and post-test odds) = Odds are defined as the probability of a certain event occurring (P) divided by the probability of that event not occurring (1-P). Therefore, it is possible to convert pretest probability to pretest odd and posttest odd to post probability. The great advantage of using odds is the possibility of direct calculation of posttest odds and therefore posttest probabilities using LRs.¹
- Diagnostic odds ratio (DOR) = $+LR/-LR$

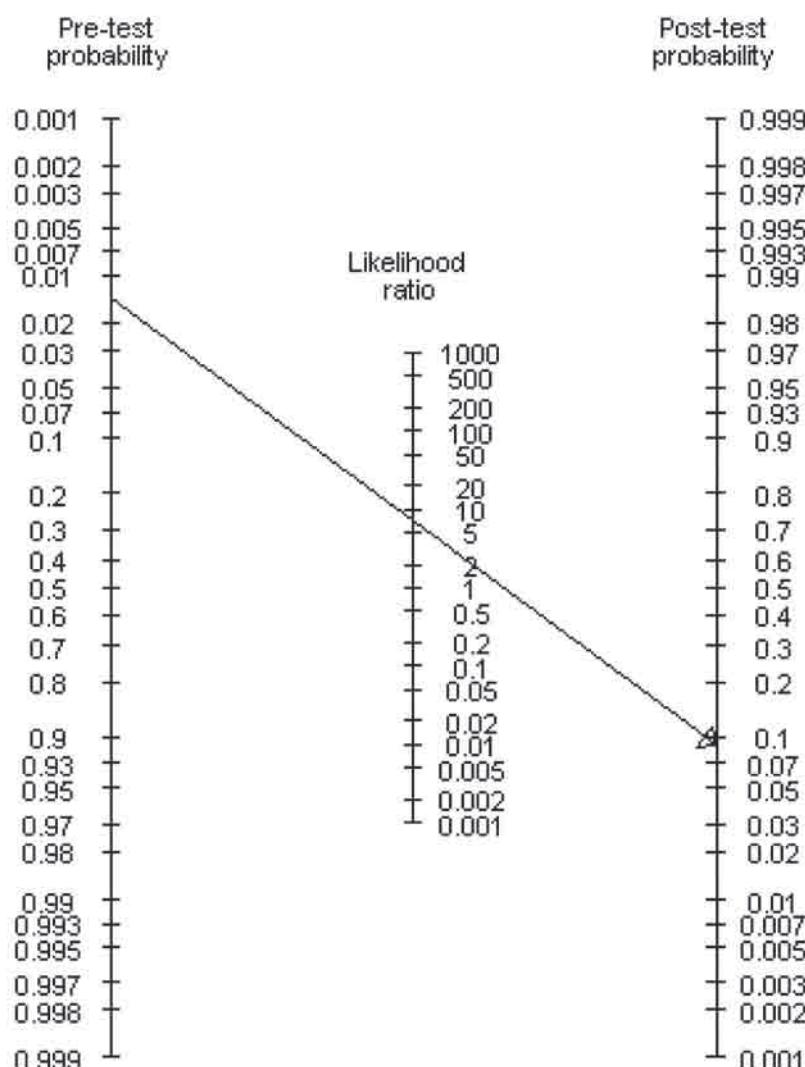
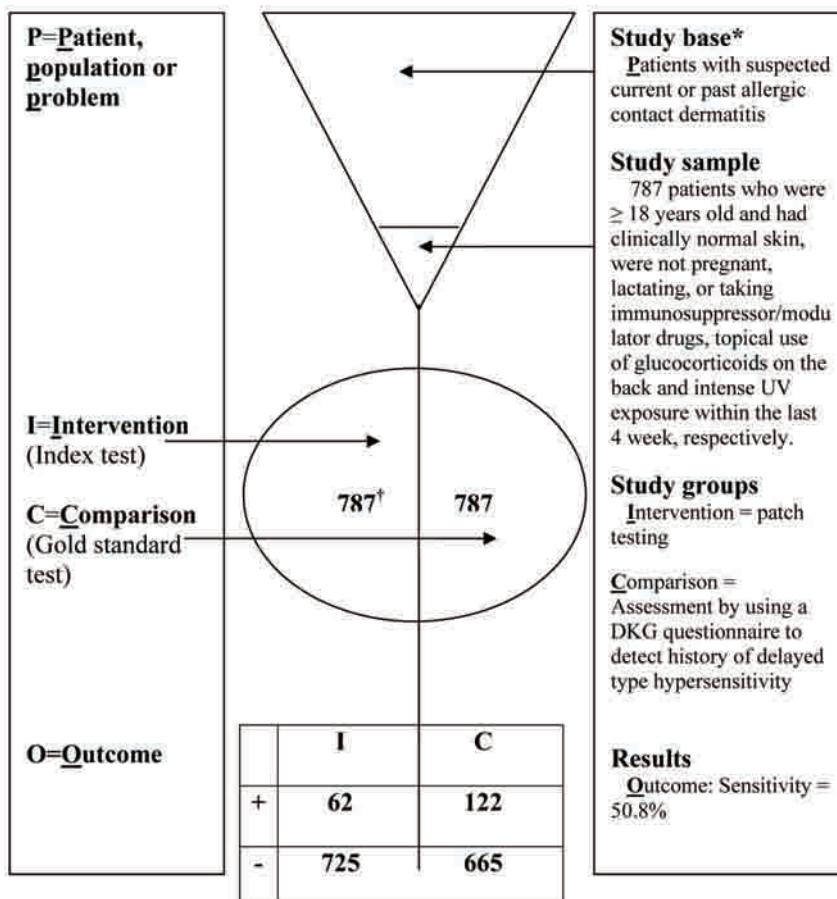


FIGURE 1-2 A Fagan plot or Bayes nomogram for calculating post-test probability when pretest probability and the likelihood ratio of a diagnostic test are known. To use this plot, a straight line should be drawn from the pre-test probability of a condition to the likelihood ratio of the test. This line should be continued until it intersects the post-test probability. This point shows the post-test probability.

It can be read as either the ratio of odds of positivity in disease relative to odds of positivity in non-diseased or the ratio of the odds of disease in test positives relative to odds of disease in test negatives.¹⁸

- Receiver Operating Characteristics (ROC) curve = This measure is suitable when a diagnostic test has different cut points for presence of a certain condition (e.g., disease). This curve is produced by scatter plotting of sensitivity against 1-specificity of different cut points of a diagnostic test. In ROC curve method, the area under the curve (AUC) is used to measure the performance of the test. Similar to LRs, ROC curve combines sensitivity and specificity to measure the test accuracy.

The most commonly utilized indices to assess the performance of a diagnostic test are “sensitivity” and “specificity.” If they were both more than 80%, because of the rule of thumb, the test could be considered as a good one. However, it is obvious that the performance of a test highly depends on the aim of its use. Other outcomes such as PPV and NPV as well as likelihood ratio and consequently diagnostic odds ratio can be used for assessment of the accuracy of the test. PPV and NPV, in contrast to sensitivity and specificity, depend on the prevalence (pretest probability) of the condition of interest in the population. If a ROC curve is to be used, a test with an AUC more than 80% is usually considered as a “good” test.¹⁷



EVIDENCE-BASED APPROACH TO DIAGNOSTIC STUDIES

Principles of evidence-based approach to diagnostic studies are not different from evidence-based approach to other types of studies. They are:

1. Framing a well-built answerable clinical question
2. Searching for the current best evidence systematically
3. Appraising the found evidence critically
4. Applying the evidence to the patient
5. Evaluation of the previous steps

The following sections mainly focus on the first three steps of EBM and the chapter is continued with a discussion about systematic reviews on diagnostic test accuracy.

A Well-Built Clinical Question

Evidence-based approach to diagnostic studies always starts with a well-built clinical question. EBM pioneers suggested the use of PICO acronym, which represents Population/Intervention, Comparison, and Outcome. It is appropriate for formulating questions concerning diagnostic studies.^{19,20} Figure 1-3 shows PICO components for a question about a diagnostic test using graphic appraisal tool for epidemiologic studies (GATE). It visualizes the

FIGURE 1-3 Graphic presentation of PICO components in a clinical question concerning a diagnostic test using a GATE frame. One advantage of using a GATE frame is that it facilitates framing the steps of EBM through using a picture. UV, ultraviolet; DKG, German Contact Dermatitis Research Group. *The exemplary study is based on the data from parts of a study by Dickel et al.²² † The total number of participants in this study was 787. ALL participants have tested by both intervention (index) and comparison (gold or reference standard) tests.

critical appraisal.²¹ The first step in a diagnostic systematic review is also asking a well-built clinical question. More details will be provided on characteristics of each PICO component at the critical appraisal section.

Hierarchy of Evidence in Diagnostic Studies

Herein, the hierarchy of evidence for diagnostic studies from different dimensions will be discussed. It has been well established that the highest level of evidence in therapeutic studies is systematic review of homogeneous randomized controlled trials (RCTs) followed by high-quality individual RCT. The hierarchy of evidence for diagnostic studies is not that much straightforward.^{5,19} Part of this complexity is related to what is considered as “*hierarchical model of efficacy*” of diagnostic studies (Table 1-2).¹⁹ For the sake of simplicity, we will only discuss the hierarchy of evidence concerning studies on diagnostic test accuracy in this chapter.

It has been generally agreed that the best study design for diagnostic accuracy assessment of a test is cross-sectional. Such a study is conducted on a random or consecutive sample of patients (or suspicious patients). ALL participants would undergo a blind comparison using both index and gold standard tests.^{19,21} Index test is the test, which is under study. The gold standard, which is also known as gold standard, is the most accurate available test for determining the presence or absence of the condition of interest.²³ There are three main reasons for assessing the accuracy of an index test: (1) replacement: which means that a new test is to be replaced an existing test, (2) triage: which means that the new test is planned to assist to make decision on whether the existing test is indicated or not, and (3) add-on: which means that the new test would be performed to provide more information on the tested individual after the existing test was performed.²⁴ In Tables 1-3 and 1-4, we provide two hierarchies of evidence for diagnostic test studies. The former (Table 1-3) is not limited to the studies on diagnostic test accuracy, but the latter (Table 1-4) is.^{22,25}

TABLE 1-2—Hierarchy Model of Efficacy in Diagnostic Test Studies¹⁹

Level	Assessed efficacy	Example(s)
1	Technical	Quality of image produced by a digital dermoscopic system
2	Diagnostic accuracy	Sensitivity and specificity
3	Diagnostic thinking	+LR and -LR
4	Therapeutic	Decisions concerning changes in the treatment of patients according to the test result
5	Patient outcome	Quality of life
6	Societal efficacy	Cost-effectiveness

TABLE 1-3—Hierarchy (Strength) of Evidence in Diagnostic Tests Studies

Level of evidence	Study type
1a	Systematic review with homogeneity of level 1b studies
1b	Validating cohort study with good reference standard
1c	Absolute SPins* and SNouts†
2a	Systematic review with homogeneity of level 2b studies
2b	Exploratory cohort study
2c	Outcome researches
3a	Systematic review with homogeneity of level 3b studies
3b	Nonconsecutive studies or without consistently applied reference standard
4	Case series or poor or nonindependent reference standard
5	Expert opinion without critical appraisal

*Specificity rules positives in, †Sensitivity rules negatives out.
(Adapted from the Oxford Center for Evidence-Based Medicine website.²⁵)

Searching for Diagnostic Studies

The second step in EBM, is performing a well-defined “search.” Two elements are crucial to perform a productive search: (a) resources: which is related to “where” someone has to look for the best evidence, and (b) search strategy: which determines how someone has to look for the evidence.

TABLE 1-4—Hierarchy (Strength) of Evidence in Diagnostic Test Accuracy Studies with Regard to Bias-Freeness

Level	Study type
I	A systematic review of level II studies
II	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among consecutive persons with a defined clinical presentation
III-1	A study of test accuracy with: an independent, blinded comparison with a valid reference standard, among non-consecutive persons with a defined clinical presentation
III-2	A comparison with reference standard that does not meet the criteria required for Level II and Level III-1 evidence
III-3	Diagnostic case control studies
IV	Study of diagnostic yield (no reference standard)

*Specificity rules positives in, †Sensitivity rules negatives out.
(Adapted from Merlin et al.²³)

Resources

It is difficult to provide a flawless summary of information sources because of their diversity. However, we recommend starting with some of the popular and easy to search electronic databases in medical sciences such as PubMed, MEDLINE, EMBASE, ISI Web of Knowledge and MD Consult.²⁶ Furthermore, SCOPUS can be used as one of the most comprehensive databases. There are some databases like Meta-analyses van Diagnostisch Onderzoek (MEDION), which specifically indexes diagnostic studies.²⁷ If the aim of the search is to look for secondary evidence such as systematic reviews following databases will be useful: Cochrane Library including the Database of Abstracts of Reviews of Effects (DARE) and Cochrane Central Register of Controlled Clinical Trials (CENTRAL), Turning Research Into Practice (TRIP) database, and databases available from Center for Review and Dissemination (CRD) at University of York, UK including Health Technology Assessment (HTA) database.²⁸⁻³⁰ Certain utilities such as Clinical Queries in PubMed are also helpful to locate systematic reviews.³¹

Another important resource is the so-called “grey literature” which encompasses resources that are not usually found through searching books, articles, and aforementioned databases. These include dissertations, research reports from governmental or non-governmental organizations, institutes and companies, and most conference abstracts and proceedings. There were two databases known as the European Association for Grey Literature Exploitation (EAGLE) and System for Information on Grey Literature (SIGLE), which are widely used for searching grey literature. Currently, OpenSIGLE which has been launched by Institute for Scientific and Technical Information–National Centre for Scientific Research covers all former records of SIGLE as well as the data added by

EAGLE members.³² A well-built list of main electronic databases with their URL addresses is provided by Kelly.²⁶

Search Strategy

The search strategy is dictated by the well-built explicit clinical question, which reflects the aim of the study. Some publications defined sensitive and specific search strategies for locating diagnostic studies.^{33,34} Table 1-5 shows the differences between the most sensitive, the most specific, and the most accurate search strategies in MEDLINE to find diagnostic studies in family medicine journals. Validity of each search strategy is based on its DOR.²⁵ It is important to remember that sensitivity and specificity of search strategies are different in various databases. Bachmann and his colleagues developed accurate search strategies to locate diagnostic accuracy studies in EMBASE.³⁴ Nevertheless, experts argue against routine use of predefined electronic filters for retrieving studies on diagnostic test accuracy.^{32,35}

Developing a proper structure based on the main components of the clinical question is another approach. The following is an example from Cochrane Collaboration.³⁵ Eisinga starts building the search structures by keeping the main components of the review question (i.e. index test(s), target condition, gold standard, and patient description). The first two components have to be used in all search structures, which she suggests. Eisinga's search structures are:

- Index test(s) AND target condition
- Index test(s) AND target condition AND patient description
- (Index test(s) OR reference standard) AND target condition
- (Index test(s) OR reference standard) AND target condition AND patient description

TABLE 1-5—Examples of Search Strategies for MEDLINE to Locate Diagnostic Test Accuracy Studies in the Journals Concerning Family Medicine³³

Content of the search strategy	Characteristic of the strategy	Sensitivity % (95 % CI)	Specificity % (95 % CI)	DOR % (95 % CI)
Sensitivity and specificity (exploded) (sh) Specificity (tw) False negative (tw)	Most accurate	73.3 (63.3-83.3)	98.4 (97.9-98.9)	170
Sensitivity and specificity (exploded) (sh) Specificity (tw) False negative (tw) Accuracy (tw) Screening (tw)	Most sensitive	89.3 (82.3-96.3)	91.9 (90.8-93.0)	95
Sensitivity and specificity (exploded) (sh) Specificity (tw)	Most specific	70.7 (60.4-81.0)	98.5 (98.0-98.9)	158

CI, Confidence interval; DOR, Diagnostic odds ratio sh, MEDLINE subheading;
tw, text word

To increase the sensitivity of these searches, which may cost the precision of them she recommends using: (1) a range of terms including text words and subject headings like MeSH, (2) advanced search techniques for example “explode” subject headings to retrieve more specific terms, (3) synonyms, related terms, variant spellings, acronyms, abbreviations, and (4) truncation and wildcards. To increase the precision of the search she suggests: (1) proper use of limits (e.g. limiting to “human” studies) (2) excluding irrelevant publication types (e.g., case reports), (3) Careful use of proximity operators, where available, and (4) use of subheadings with specific subject headings.

As an example, Dwamena has built a search structure based on second Eisinga's platform. Dwamena described a four-step search method in MEDLINE. He suggested a combination of Boolean operators including “OR” and “AND” as well as all subheadings of conditions and tests of interest through “Explode”, truncation and wildcards to find diagnostic studies². The steps are as follows: (1) searching for population, which is based on methods and criteria for the selection of the study population, (2) adding the “index test” to the previous search, (3) adding the outcome of interest or target condition, and (4) restricting the result of the third step by limiting it to for example “humans,” etc. He has used “breast cancer” as an example to demonstrate the functionality of this four-step search. He could locate 108 potentially eligible studies out of 181132 citations that he found at the end of the first step of his search.² More explicit information on searching the evidence is available in the *Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy* and is highly recommended for those who intend to perform a systematic review on diagnostic test accuracy.³²

Critical Appraisal (Quality Assessment) of Studies on Diagnostic Test Accuracy

Like all other studies, diagnostic test accuracy studies may be affected by biases or variations.^{13,34} It is of paramount importance to assess a diagnostic accuracy study with regard to potential variations and biases. Common biases in diagnostic accuracy are as follows.^{16,36-38}

Patient-related biases are related to recruitment in studies:

Spectrum bias

To investigate the risk of this bias in a study, two important issues should be considered: (1) recruitment of a suitable group of patients for the study, and (2) use of a proper sampling method. The main issues concerning the recruited patients are demographic characteristics, such as patients' age, and the clinical characteristics of their disease, such as its severity. It is also important that the spectrum include patients suffering from diseases that can

be differentiated from the disease of interest. These issues may be influenced by the study setting, eligibility (i.e., inclusion and exclusion criteria), and design issues. Biases caused by improper definition of eligibility criteria are one of the main concerns in this field. Limited challenge bias is a specific type of spectrum bias. This form of bias occurs when diagnostically difficult cases are not included in the study, and it leads to overestimation of test characteristics such as the sensitivity and specificity of the index test. In a diagnostic case-control study, the accuracy of the index test would be assessed between healthy controls and a group of patients, and it is easy to understand that such a design would overestimate the accuracy of the test that is being evaluated.

Selection bias

A prospective consecutive sampling of patients who meet eligibility criteria for the study is recommended. A random sample of eligible patients may also be considered. If the patients who are recruited for the study have not been chosen through appropriate sampling methods, then the study will be prone to selection bias.³⁶

If the diagnostic study does not recruit the subjects randomly (demonstrating selection bias) and there is a trend toward selecting patients with more severe disease (spectrum bias), then this would boost the assessed accuracy of the index test.

Another source of bias is test-related issues. Although information bias can be caused by issues related to the gold standard or index test, other biases are caused only by the gold standard test. These biases include:

Information bias

Awareness of the results of either the index test or the gold standard test before knowing the results of the other test can influence the results of the second test. The resultant bias is called test review bias or diagnostic review bias. Proper blinding of the interpreters can control this bias.

Asymmetric awareness of clinical information at the time of interpretation of either test may also cause a similar form of bias known as clinical review bias. In this context, “asymmetric information” refers to the fact that one of the diagnostic tests is performed and/or interpreted in the presence of more clinical information, while no such information is available within the other test(s), including the gold standard or routine practice. Information bias usually results in overestimation of the accuracy of the test.

Misclassification bias

This bias occurs when the gold standard test cannot accurately differentiate between those who have the condition of interest and those who do not. Hence, it will misclassify study participants. The effect of this bias on the accuracy of

the index test depends on whether the index test causes the same error.^{36,37}

Partial verification bias

This bias occurs when patients with a positive index test are more likely to be referred for the gold standard and therefore to be included in the study. In these circumstances, the result of the index test is the basis for cross-verification with the gold standard. This bias is also known as primary selection bias, work-up bias, and sequential order bias.³⁸ This bias leads to overestimation of sensitivity with variable effects on specificity.

Differential verification (double gold standard) bias

This bias occurs when a part of the index results is verified by another gold standard. In this bias, some patients will receive gold standard 1 and the other gold standard 2, while all will undergo the index test. This usually results in overestimation of test accuracy.

Incorporation bias

This bias occurs when index and gold standard tests are not completely independent. Hence, the index test is used to establish a final diagnosis and is therefore effectively a part of the gold standard. Incorporation bias usually leads to overestimation of the diagnostic accuracy of the test.

Another group of biases is caused by changes in the disease because of a long delay between administration of the index and gold standard tests.

Biases caused by changes in disease

If the time for cross validation between the index test and gold standard test is too long, the severity of the disease may change, and these changes may produce a different result for the test that is performed later. These changes may be categorized into three major groups: (1) increase in the severity of disease, which is known as disease progression bias and is associated with more severe disease at the time of performing the latter test, (2) recovery bias, which is caused by recovery or improvement of the disease during the interval between performance of the tests, and (3) treatment paradox bias, which occurs when patients receive a therapeutic intervention after administration of the first test that results in cure or improvement of their disease. Both disease recovery bias and treatment paradox bias are associated with less severe disease at the time of administration of the second test. Assuming that the patients were first assessed by the index test, the accuracy of the index test will be underestimated because of disease progression

bias and overestimated because of disease recovery and treatment paradox biases.

Leeflong and colleagues have considered “excluded data” as a potential source of bias, usually leading to overestimation of the accuracy of a test.³⁶

In addition to withdrawals and uninterpretable test results, which may be covered under biases caused by data exclusion, the sponsorship of a study should also be considered at the time of the quality-assessment process.

Whiting et al. have correctly stated that the distinction between bias and variation is not always clear. Therefore, they consider almost all potential errors deriving from the patients (population) as variations. They also identify errors caused by test execution, test technology, and observer variability as variations.¹⁶

To help achieve this stage of EBM, several tools have been developed.^{39,40} As recommended by the Cochrane Handbook of Systematic Reviews of Diagnostic Test Accuracy Studies, items of Quality Assessment of Diagnostic Test Accuracy Studies (QUADAS) may be used for quality assessment of individual studies.³⁹ Since its development, QUADAS has been commonly used for assessing the quality of eligible studies in several systematic reviews of diagnostic tests and its application has also been evaluated.⁴¹ QUADAS has an important advantage: it does not rely on summary score points.⁴¹ Commenting on the adequacy of each assessed item is strongly recommended.³⁶

High-quality reporting of a study is necessary if a valid quality assessment is to be performed. The quality of reporting of the accuracy of diagnostic tests was less than optimal and required improvement. For this reason, a group of experts in this field launched the Standards for Reporting of Diagnostic Accuracy (STARD) initiative, resulting in a 25-item checklist and a flowchart.^{42,43} STARD is a counterpart to the better known Consolidated Standards on Reporting Trials (CONSORT) checklist and flowchart, which was developed before STARD to improve the quality of reporting of clinical trials.⁴⁴

DIAGNOSTIC SYSTEMATIC REVIEWS: GENERAL ISSUES

The distinguishing difference between a systematic review and a narrative review is a systematic approach to the relevant literature in the former. Indeed, the very first stage of performing a systematic review is to develop a protocol. The systematic review should be conducted according to this protocol. So in contrast to a narrative review, all steps of conducting a systematic review including its aim and objectives, eligibility (i.e., inclusion and exclusion) criteria for the studies, and search strategy are pre-defined. Systematic reviews on diagnostic test accuracy follow the same track. It is expected that the authors of a systematic review clearly state these issues in their review. The main components of a diagnostic systematic review report are

introduction, aim and objectives, methods, results, discussion and conclusion.

Introduction

This part summarizes the important “knowns” and “unknowns” about the subject of the study and contains the rationale for performing the systematic review. Introduction usually ends with uttering the aim and objectives of the systematic review.

Aim and Objectives

This part reflects the well-built clinical question and may mention either explicitly or implicitly. It may become a separate section or could be incorporated in different parts of the introduction and/or search strategy.

Methods

Search strategy

A clear and repeatable search strategy is an essential component of any type of systematic review. It should contain all the used “keywords”. If there are different search strategies for different databases, it should be explicitly addressed. The limits of the search should also be included in the search strategy.

Resources

All resources including electronic databases, hand-searched journals, and any material from so-called grey literature should be clearly addressed.

Selection of studies

The eligibility criteria for inclusion and exclusion of the studies should be defined beforehand and have to be followed meticulously. The author(s) of a systematic review should state clearly how they have looked for eligible studies. Important issues to be looked for in the “selection of studies” and part of a systematic review are study design, participants, target condition, and index, comparator and gold standard tests. The most common method for study selection is to review the titles and abstracts (when available) of the retrieved articles rapidly and decide about their eligibility based on the provided information in those part of the articles. If the authors do not find this information for decision-making, then the most reliable act is to obtain the full-text of the article to judge about the existing uncertainty. Two members of the systematic review team usually do this step independently and then the results will be discussed together. If they do not agree on few titles or abstracts, full-text of all articles with questionable eligibility

may be found and reviewed. An alternative approach is to ask a third reviewer for final decision making, particularly when the number of the debatable articles is large.

Data extraction

It is important that the authors of a systematic review mention how they extracted the data from the included primary studies. It is also expected to be done based on an a posteriori plan. Data extraction forms should be developed according to the quality assessment tools.³⁶ Appropriate data extraction is a prerequisite for a valid critical appraisal. Again, it is suggested that two independent reviewers do the data extraction.

Quality assessment (critical appraisal)

As it has already mentioned in this chapter, critical appraisal of the quality of individual studies is crucial for performing a valid systematic review. In order to perform this step, the authors of a systematic review should consider all questions concerning the qualities of included studies beforehand and clearly address them.

Methods for exploring heterogeneity of the studies

There are several reasons for heterogeneity in different studies of the same topic. They include (a) design-related issues such as limiting the biases and confounders, (b) differences in patient selection, (c) baseline disease severity, and (d) definitions of outcome measures.⁴⁵ With regard to diagnostic accuracy test studies, an important cause of heterogeneity is known as “threshold effect.” This effect occurs when different cut-offs (thresholds) are considered for determining sensitivity, specificity, and likelihood ratios in different studies. When threshold effect exists, a negative relation between sensitivity and specificity and a positive relation between sensitivity and 1-specificity exists.^{3,46,47} In general, heterogeneity in included studies of a diagnostic systemic review is a rule rather than an exception.⁴⁸ This fact cannot prevent pooling the data from heterogeneous studies, unless the heterogeneity would be statistically significant. Thus, exploration of heterogeneity should be clearly sought and explained.

Methods for pooling of the data: systematic review versus meta-analysis

A plan for pooling the data including the summary outcomes should be clearly stated. As a reminder, systematic review and meta-analysis are two different types of studies: while systematic review is a systematic search of evidence through predefined criteria, meta-analysis is the statistical method for combining results from different

studies and providing outcome summaries. Therefore, systematic reviews do not need to contain meta-analyses and meta-analyses are not necessarily performed on the studies in systematic reviews.

Meta-analysis

The ultimate goal of a meta-analysis is to give an overall summary coherent with all observed data (i.e., findings of the included studies). This summary should be highly precise. To accomplish this goal, a weighted average of the effect size of studies is typically used. The rationale for it is that the larger studies are more informative. Deviations of studies from the overall summary should be explored and reasons for such deviations are expected to be explained.⁴⁸

Traditionally, two statistical models were used to perform meta-analysis in a therapeutic systematic review: fixed-effects and random-effects methods. While in fixed-effects model, the inference is conditional on the studies actually done, in the random-effects models, the inference is based on the assumption that the studies, which are included in the analysis, constitute a random sample of some hypothetical population of studies.⁴³ Examples of fixed-effects models analyses are Mantel-Haenszel and Peto methods. One of the most famous examples of random-model analyses is DerSimonian and Laird method. This brief discussion about the fixed- and random-effects models can give the readership some acquaintance with what is mentioned about meta-analysis methods for diagnostic test accuracy studies. However, the monograph in epidemiology and biostatistics, by Petitti, has provided an interesting discussion on the difference between the two models. We recommend reading it to those who would like to obtain more information on this subject.⁴⁵

When meta-analysis for diagnostic accuracy studies is planned, it is important to remember that commonly used characteristics of the test performance such as sensitivity and specificity and positive and negative likelihood ratios are paired. DOR is an exception and is summarized as a single measure. SROCs are also among most frequently reported summary measures in this kind of systematic reviews.

Harbord and his colleagues discussed six methods for meta-analysis of diagnostic accuracy studies.⁴⁹ The first four methods are frequently used and simple:

1. Simple pooling (a fixed-effect method)
2. Separate random-effects meta-analyses of sensitivity and specificity
3. Separate random-effect methods of positive and negative likelihood ratios
4. Littenberg-Moses summary receiver operating characteristics (ROC) curve

They also considered two more statistically rigorous methods known as:

5. Bivariate random-effects meta-analysis
6. Hierarchical summary ROC curve analysis

These rigorous methods are both based on hierarchical models.

Detailed discussion about the characteristics of these models is beyond the scope of this chapter. Briefly, they have recommended using the hierarchical methods for doing meta-analysis in diagnostic test accuracy studies as the standard methods.⁴⁹

Information about techniques for evaluation of publication bias should also be provided in the report.

Results

Several parts may be present in the “results” section of a diagnostic systematic review. Some parts may be only applicable to those systematic reviews that do not contain a meta-analysis.

Exploring heterogeneity

Appropriateness of pooling the data and the possibility of performing a meta-analysis has to be addressed at this part of a systematic review.

It is important to look for the description of pooling the data. Homogeneity of the studies can be explored using graphs, but its existence should be confirmed by performing statistical tests. Like therapeutic systematic reviews, I-squared (I^2) may be used as a measure for assessing the existing heterogeneity. I^2 measures the amount of variability caused by heterogeneity.⁴⁹ There are other methods which have been used for assessing heterogeneity in meta-analysis, including Cochrane Q and G^2 .^{46,50} Usually small numbers of studies are included in a diagnostic test accuracy systematic review, so either Cochrane Q or G^2 has low power and is frequently unable to detect the existing heterogeneity.⁴⁶ If the studies are too heterogeneous to be pooled in one or more groups, summary estimates of the results may be misleading and a clear simple statement of each study characteristics would be more appropriate.

Summary of quality assessment of the included studies

Using QUADAS for the quality assessment of the included studies in a systematic review has been discussed in earlier parts of this chapter.³⁹ It is also possible to demonstrate a quantitative summary of the quality assessment results for those studies by making bar charts based on the items recommended by QUADAS for that process (Figure 1-4).^{36,39}

Summary of pooled data

The Littenberg-Moses method, which was used in 34 diagnostic tests accuracy systematic reviews, is the most

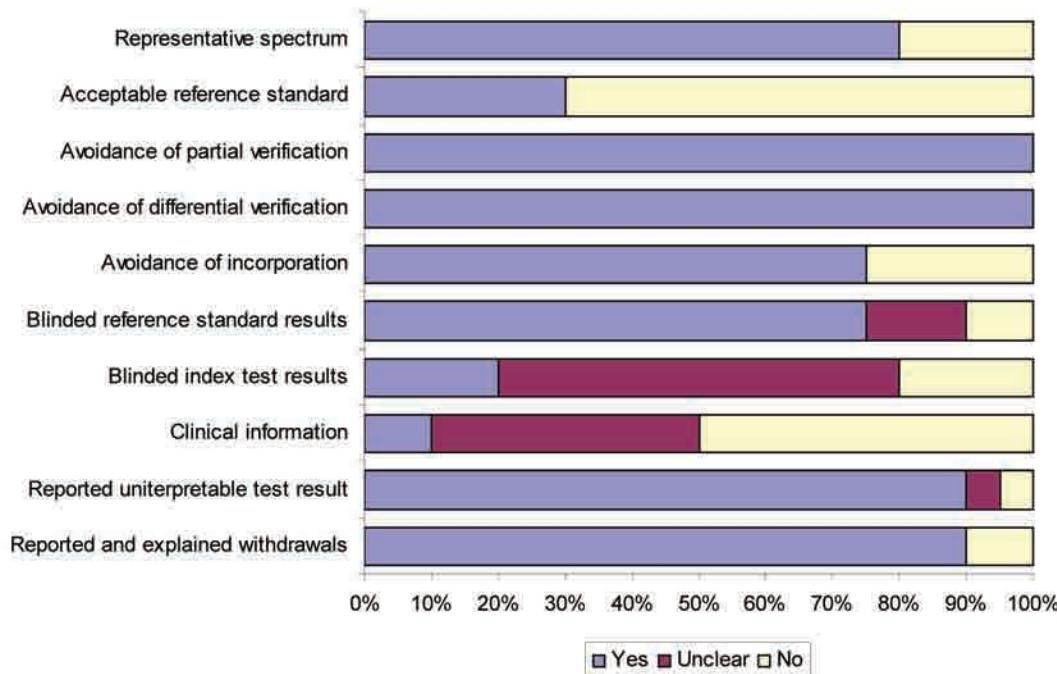


FIGURE 1-4 An exemplary bar chart based on simulated data, which is commonly used to summarize the results of quality assessment of primary studies in a diagnostic test accuracy systematic review based on some items of QUADAS. Each bar represents a certain item in QUADAS. Please notice that it is assumed that not all QUADAS items have been assessed. Data are presented as percentage of included studies.

common (41%) method for providing summary measure.⁴⁹ Meta-analysis of likelihood ratios and summary of predictive values derived from meta-analysis of likelihood ratios (29%) were the second most commonly used summaries. It is also possible to provide summaries of sensitivity and specificity as well as DOR.^{16,49} Please notice that simple pooling of sensitivity and specificity is usually inappropriate because this approach ignores threshold difference. At this section, we will provide a brief description of graphic techniques used in demonstrating these test accuracy summaries with some examples.

- Forest plots:** These plots are among commonly used graphs for displaying results of a meta-analysis. Point estimates of individual studies are shown as points or boxes, which are sometimes proportional to the sample size of each study. Confidence intervals are shown as horizontal lines. Summary of the pooled data is commonly demonstrated as a diamond, which the center represents the point summary estimate and its tips shows the confidence interval.^{51,52}

Forest plots are informative and easy to understand. In diagnostic tests, accuracy studies, the outcomes of interests are usually in pairs (i.e. sensitivity and specificity, positive predictive value and negative predictive value, and likelihood ratio for a positive test and likelihood ratio for a negative test). This is why forest plots come in pairs for diagnostic studies. DOR is an exception and a single forest plot is enough for showing characteristics of different studies. The summary DOR

should be calculated from sensitivities and specificities of each individual included in the study, not from the pooled sensitivity and specificity of those studies. Using the free downloadable software Meta-DiSc version 1.4,^{47,48} we drew forest plots for sensitivity and specificity, positive and negative likelihood ratios, and DOR with simulated data from 12 imaginary diagnostic test studies (Figures 1-5, 1-6 and 1-7).

2. Summary Receiver Operating Characteristics (SROC) curve

We drew a SROC with simulated data from 12 imaginary diagnostic test studies using “Meta-DiSc”,⁴⁷ (Figure 1-8). The Littenberg-Moses method was applied in Meta DiSc to draw this graph.

- Information on publication bias.** The most common way to present the publication bias is to use a funnel plot. However, it is important to mention that while a funnel plot can potentially facilitate visual detection of the publication bias, statistical techniques are needed for precise interpretation of the data. Diagnostic log odds ratio can be used as the measure for study precision and 1/square root of effective sample size can be applied as the measure for its effect size. A proper regression analysis may be used for detection of statistical significance. Usually a P smaller than 0.1 is considered as significant for the slope coefficient of the regression line.^{2,53} However, some experts in diagnostic systematic reviews mention that these methods of statistical assessment are not proper for assessing publication bias in this type of systematic reviews.³²

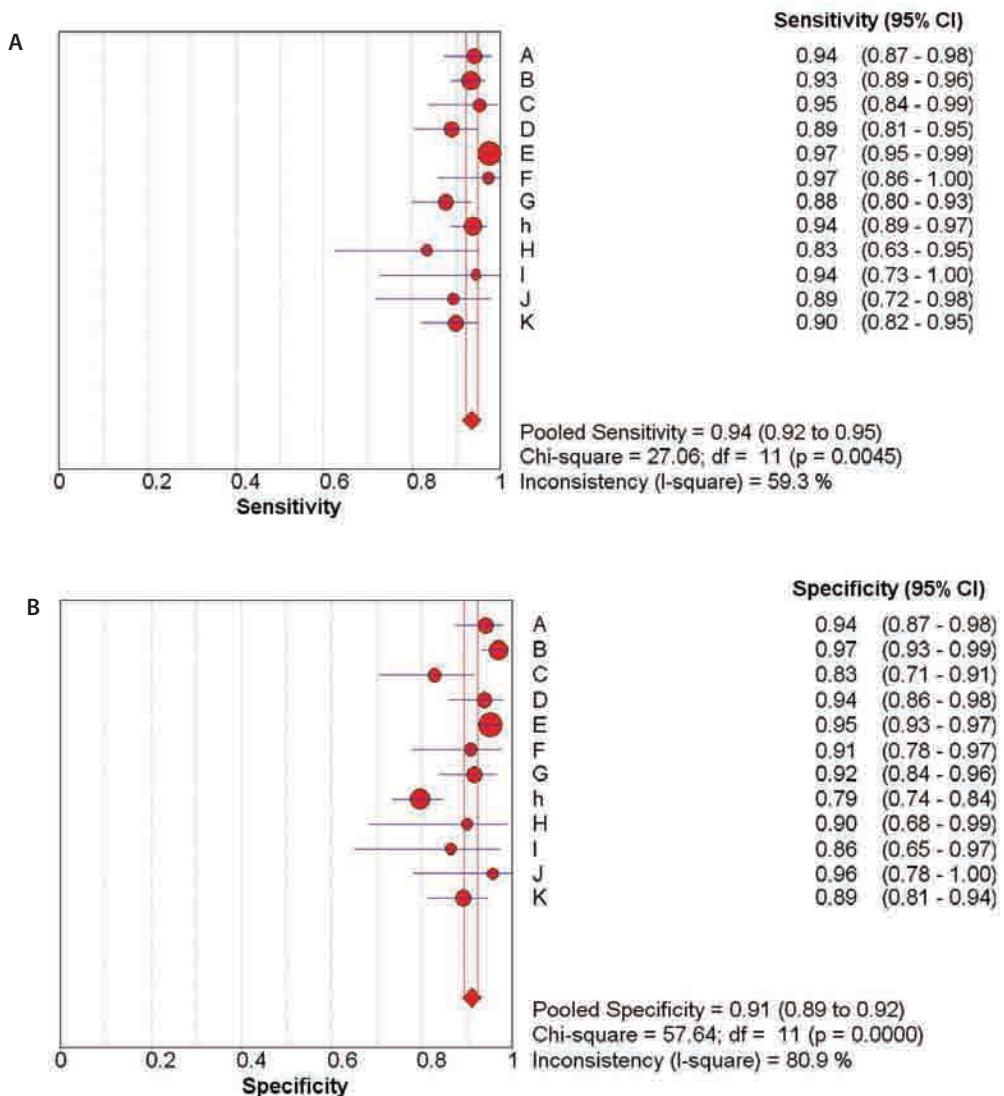


FIGURE 1-5 Paired forest plots of a simulated diagnostic test accuracy systematic review.
(A) Sensitivity. (B) Specificity. Graphs have been drawn using Meta-DiSc software.^{47,48}

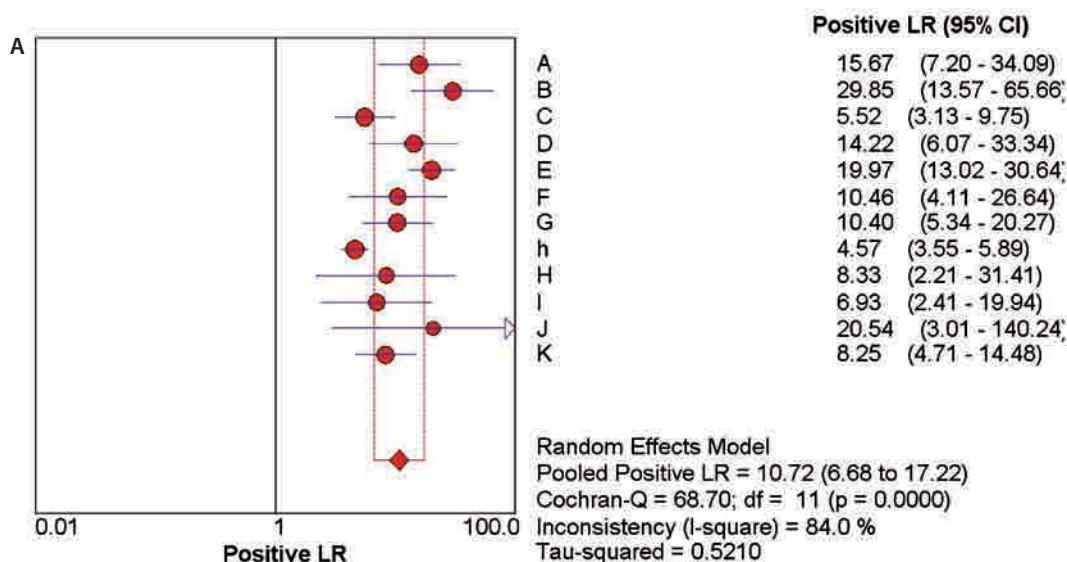


FIGURE 1-6 Paired forest plots of a simulated diagnostic test accuracy systematic review. (A) Positive likelihood ratio. (Continued)

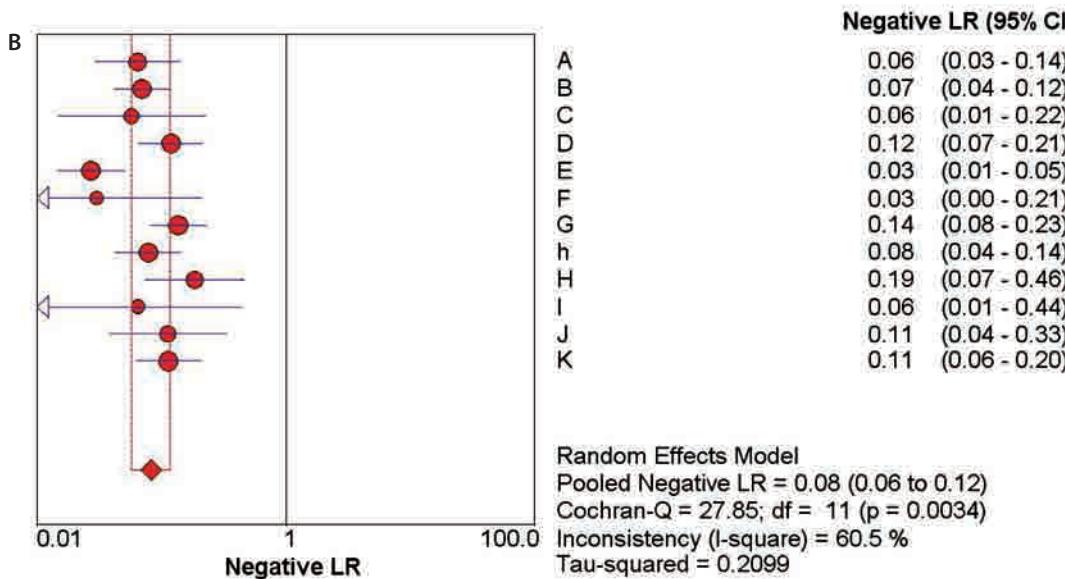


FIGURE 1-6 (Continued). (B) Negative likelihood ratio. Graphs have been drawn using Meta-DiSc software.^{47,48}

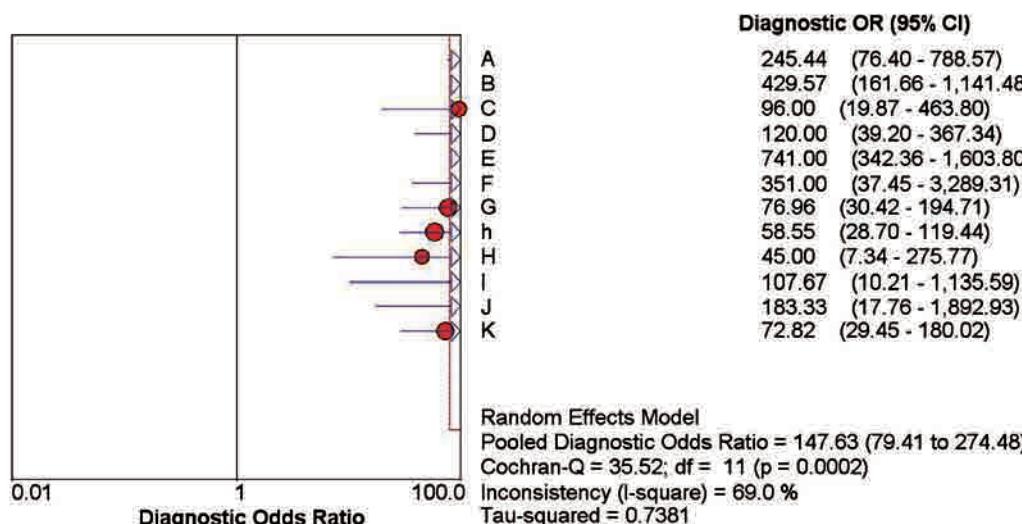


FIGURE 1-7 Summary diagnostic odds ratio (DOR) (forest plot) of 12 fictional diagnostic accuracy studies included in a simulated systematic review. Graph has been drawn using Meta-DiSc software.^{47,48}

Discussion

A detailed discussion of all findings of the review should be provided in this section. It means that findings of each individual included study as well as the findings of the whole systematic review should be discussed. For this purpose, the results of the conducted review should be compared to previous literature and any differences should be explained. The reasons for supporting the findings should be discussed as well. Limitations and shortcomings of the review as well as their influences on the review's validity should be stated. Comments should be helpful for clinical practice and designing future studies.

Conclusion

The bottom line of the review is expected to be found in this section of a systematic review. It should contain the paramount findings and very brief explanations for these findings. In addition, potential application of this new evidence in practice and research should be briefly stated. The conclusion section should be limited to a few paragraphs at most.

DIAGNOSTIC SYSTEMATIC REVIEWS IN DERMATOLOGY

It seems that diagnostic systematic reviews are still at their early stages in dermatology. Several chapters in this book

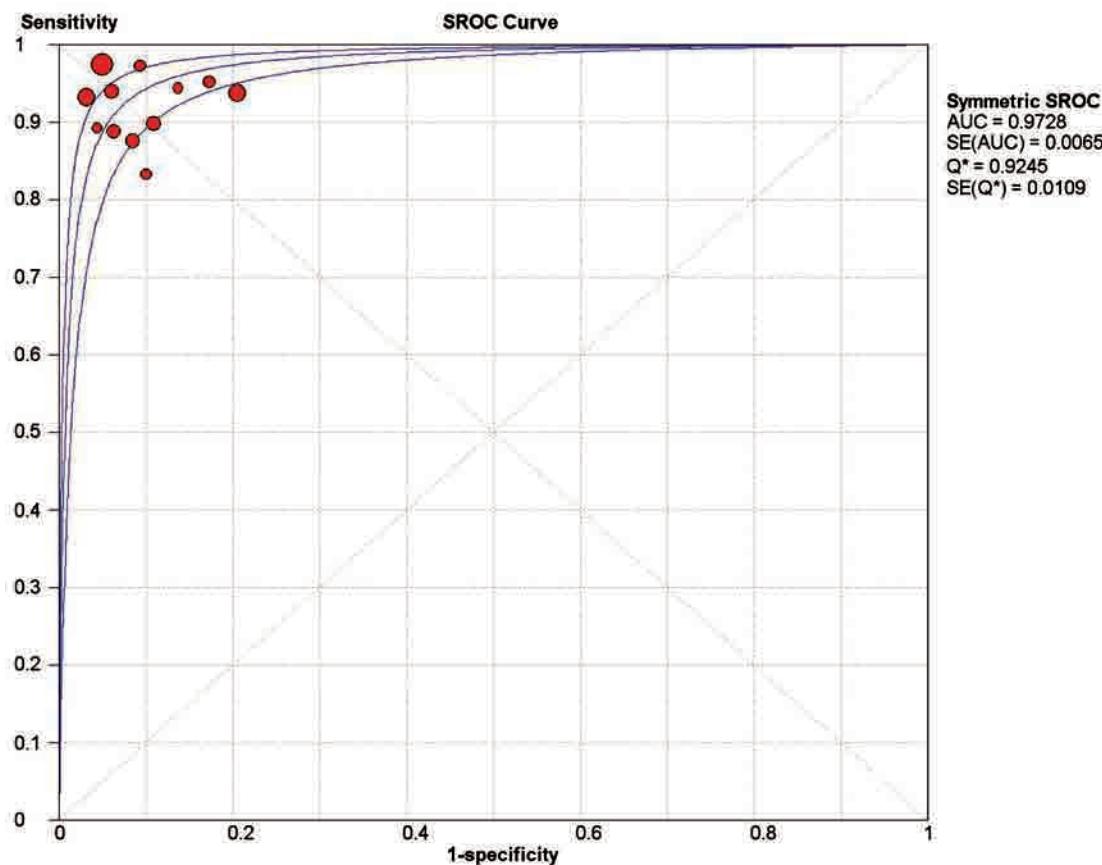


FIGURE 1-8 SROC curve of a simulated diagnostic test accuracy systematic review. This graph has been drawn using Meta-DiSc software.^{47,48}

(Chapters 2-9) provide evidence-based information on some diagnostic methods, which are used in dermatology for important diseases such as malignant melanoma, hirsutism, allergic contact dermatitis, and cutaneous T cell lymphoma. Evidence for useful diagnostic modalities

such as teledermatology and patch testing has been included as well.

In recent years, systematic reviews concerning diagnostic accuracy have been published in dermatology journals such as Rajpara et al. and Brenninkmeijer et al.^{11,54}

What We Know

- Physicians want to diagnose the disease as specifically as possible to (1) explain the details of condition to the patient, (2) be aware of risk factors and prognosis of the disease, (3) develop a proper treatment strategy based on all the details.
- The general principals of EBM approach to diagnostic test studies are similar to what exists for therapeutic, preventive, and prognostic studies, as they are interconnected.
- The hierarchy of evidence in diagnostic test studies is different from the widely accepted hierarchy for therapeutic interventions.
- Searching for the evidence on diagnostic tests is not widely utilized and is different from therapeutic interventions. *Cochrane Handbook of Systematic*

Reviews of Diagnostic Test Accuracy has provided useful resources in this regard.

- Acquaintance with outcomes such as sensitivity, specificity, positive and negative predictive values, likelihood ratios, and diagnostic odds ratio is crucial to properly understand a study on diagnostic test accuracy.
- Index test performance will depend on the spectrum of disease within a study population. The ability of a test to differentiate normal volunteers from severely ill patients may be misleading when the test is applied in clinical practice and not general population. On the other hand, index test accuracy is independent of disease “prevalence.”⁵⁵

What We Know (Continued)

- Similar to therapeutic studies, studies on diagnostic test accuracy are at risk of being affected by biases. Some instruments such as QUADAS and STARD have been developed to assess the quality of included studies. Dermatologists interested in diagnostic test accuracy studies are strongly encouraged to utilize and implement these tools.
- For certain reasons such as existence of “threshold effect”, studies on diagnostic test accuracy are usually more heterogeneous than their therapeutic counterparts. This fact makes pooling and summarizing the data more complicated in comparison with therapeutic studies.
- Several commonly used summary outcomes of diagnostic test accuracy studies such as sensitivity and specificity are paired. This characteristic necessitates the use of pair forest plots to display data summaries. Additionally, it results in using SROC curves as another graphic tool to demonstrate summary outcomes in relevant meta-analyses.
- Hence, the number of primary studies on diagnostic test accuracy, as well as systematic reviews and meta-analysis of these studies is increasing in all fields including dermatology. Dermatologists need to promote their knowledge and skills in critical appraisal and application of diagnostic tests and ultimately conduct quality diagnostic studies.

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Diagnostic Accuracy of Teledermatology

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INTRODUCTION

Teledermatology is a growing field in dermatology which utilizes the innovations of communications technology to provide remote care to patients. It is a way of bridging the geographical gap between patients and providers and offers a potential solution to the problem of limited access to dermatologic care. In addition, teledermatology has the potential to increase the efficiency with which dermatologic care is delivered. Based on our review of the current literature, the evidence for the use of teledermatology in clinical practice is robust.

TELEDERMATOLOGY DELIVERY PLATFORMS

Store-and-Forward

Store-and-Forward (S&F) refers to asynchronous communications between parties (dermatologist to primary care or dermatologist to patient) involved in the care process in which clinical information (usually a medical history along with photographs of the dermatologic lesions) gathered by an individual at one location is sent to a dermatologist via communications technology, such as the internet and cellular phones, at a different location. Dermatologists receiving this information review it, at a time of their convenience, and later send back their assessment along with recommendations for treatment if indicated.

Features of S&F include: (1) dermatologists do not meet their patient in person, (2) the formation of a patient-dermatologist relationship is not typically established, and (3) dermatologists are limited by the clinical information gathered at the point of care including the quality of the photographs. The advantages to S&F include: (1) improved efficiency relative to live interactive and (2) work flow flexibility for the dermatologist. Physicians are able to view and respond to consultations at a time that is convenient for them. Also, total time spent on the S&F dermatologic consult is often less than a face-to-face dermatologic visit.¹⁻²

Live Interactive

The live interactive method of teledermatology refers to dermatologic consultation that is done where a physician

in one location can see and talk to a patient at another location via a live video conference. Dermatologists are able to take a complete history of the patient, and when it comes time for the skin examination a trained medical professional at the patient's location is able to maneuver the video camera for a proper examination. The dermatologist can interact with the health care professional during the skin examination, pointing out lesions that should be measured, photographed for archive, or biopsied. There is also an opportunity for thoughtful discussion about therapeutic options for the patient.

Features of live interactive include: (1) communication between the physician and the patient occurs in real-time, (2) tends to be less cost effective than S&F, (3) requires an interaction between clinician and participants at the point of care and therefore may be less convenient for dermatologists, and (4) typically requires more coordination between the physician and the patient to be at different places at the same time in order to meet on camera.

Both S&F and live interactive teledermatology are ways of delivering remote dermatologic care. Although each modality has unique features, neither one is considered superior to the other. A comparison of the features of S&F and live interactive teledermatology is provided in Table 2-1.

TABLE 2-1—Features of S & F And Live Interactive Teledermatology

S & F	Live Interactive
The dermatologist does not meet patient in person	Communication between the patient and the dermatologist occurs in real-time
The formation of patient-doctor relationship may not be established	It requires an interaction between the dermatologist and all participants at the point of care
The dermatologist is limited by the clinical information gathered at the point of care as well as the quality of the photographs	Typically it requires more coordination between the dermatologist and the patient in order to meet on camera at different places at the same time
It is cost-effective relative to live interactive	It tends to be less cost-effective than S & F
It allows for work flow flexibility and efficiency for the dermatologist	The length of the consult is similar to that of a regular face-to-face visit

Emerging Technologies

S&F and live interactive teledermatology mainly utilize the internet and computers as the medium for delivery of care. Although these are the primary modalities which have been clinically researched, it is important to realize that teledermatology encompasses the use of all forms of communications technology including cellular phones, personal assistant devices (PDAs), and satellite communication systems. The integration of these devices into providing dermatologic care and education is of increasing interest given the frequency with which they are used by the general public.

ANALYSIS OF THE EVIDENCE SUPPORTING TELEDERMATOLOGY AS A CARE DELIVERY PLATFORM

Comparisons of Teledermatology to Face-to-Face Care*

Following the first article on the subject of teledermatology in 1995, more than 250 publications have reported ongoing research in teledermatology around the world (PubMed search “teledermatology”). In general, individual studies in the field are variable with respect to quality of methodology, sample size, power, rigor, and analysis. In aggregate, there is a preponderance of evidence that teledermatology provides care of equivalent quality to face-to-face dermatology. Studies in this field have thus tended to focus more on the evaluation of process measures, which are vital in assessing the utility of teledermatology as a clinical tool. Whenever there is a change in the paradigm of the delivery of health care, there must be evidence to show that quality has not been sacrificed.

Studies Examining Process Measures

STUDIES ON DIAGNOSTIC RELIABILITY

Studies of diagnostic reliability evaluate the diagnostic agreement between clinic-based dermatologists and teledermatologists and explore both inter- and intraobserver reliability. Many of these studies report both complete agreement (agreement on a primary diagnosis) and partial agreement (agreement on a diagnosis within a differential). Overall, there are far more studies that evaluate S&F as a vehicle for teledermatology than live interactive (see above).

To date, studies evaluating the interobserver reliability between clinic based-dermatologists and teledermatologists using S&F technology have reported ranges from 0.41-0.97³⁻¹⁷ (Table 2-2). Studies exploring the interobserver reliability between clinic-based dermatologists and

TABLE 2-2—Interobsever Diagnostic Reliability Between Face-to-Face Dermatologists and Teledermatologists Using S & F

Reference	Complete Agreement	Partial Agreement
Kvedar (3)	0.61-0.64	0.67-0.70
Zelickson (4)	0.88	—
Lyon (5)	0.89	—
High (6)	0.64-0.77	0.81-0.89
Whited (7)	0.41-0.55	0.79-0.95
Taylor (8)	0.44-0.51	0.57-0.61
Lim (9)	0.73-0.85	0.83-0.89
Eminovic (10)	0.41	0.51
Du Moulin (11)	0.54	0.63
Mahendran (12)	0.44-0.48	0.64-0.65
Oakley (13)	0.53	0.64
Tucker (14)	0.56	0.68
Bowns (15)	0.55	—
Ebner (16)	0.71-0.76	0.90-0.97
Heffner (17)	0.82	—

Complete agreement—considers the single most likely diagnosis.

Partial agreement—considers both the single most likely diagnosis and the differential diagnosis or comparable diagnosis. (From Whited JD. Summary of the Status of Teledermatology Research.¹⁰⁵)

teledermatologists using live interactive technology have found ranges from 0.54-0.99¹⁸⁻²⁴ (Table 2-3). One study by Edison et al. used three modalities (in-clinic consultation, live interactive, and S&F) to examine a single population of 110 patients and found that complete diagnostic agreement was reported 64% of the time in all three modalities.²⁵ Interobserver reliability was 80% between the clinic-based dermatologist and live interactive teledermatologists, 73% between the clinic-based dermatologist and S&F teledermatologists, and 70% between live interactive teledermatologists and S&F teledermatologists.

TABLE 2-3—Interobserver Diagnostic Reliability Between Face-to-Face Dermatologists and Teledermatologists Using Live Interactive

Reference	Complete Agreement	Partial Agreement
Lesher (18)	0.78	0.99
Gilmour (19)	0.54	0.80
Lowitt (20)	0.80	—
Loane (21)	0.60	0.76
Phillips (22)	0.77	—
Phillips (23)	0.59	—
Nordal (24)	0.72	0.86

Complete agreement—considers the single most likely diagnosis.

Partial agreement—considers both the single most likely diagnosis and differential diagnosis. (From Whited JD. Summary of the Status of Teledermatology Research.¹⁰⁵)

*Data from this section largely from Whited JD. Summary of the Status of Teledermatology Research. Telederm SIG, ATA. 105

TABLE 2-4—Diagnostic Accuracy Rates of Face-to-Face Dermatology Consultations Compared S & F Teledermatology Consultations.

Reference	Modality	Complete Accuracy Rate	95% CI	Partial Accuracy Rate	95% CI
Whited (7)	Face-to-face	0.59-0.71	0.48-0.81	0.85	0.77-0.93
	Teledermatology	0.53-0.63	0.42-0.74	0.68-0.85	0.58-0.93
Krupinski (27)	Face-to-face	—	—	0.80-0.97	—
	Teledermatology	—	—	0.73-0.78	—
Harrison (29)	Face-to-face	—	—	—	—
	Teledermatology	0.71	—	—	—
Whited (30)	Face-to-face	0.70-0.77	—	0.80-0.92	—
	Teledermatology	0.31-0.85	—	0.85	—
Moreno-Ramirez (31)	Face-to-face	—	—	—	—
	Teledermatology	0.79	—	—	—
Oakley (32)	Face-to-face	0.72	0.53-0.83	—	—
	Teledermatology	0.71	0.56-0.83	—	—
Lozzi (33)	Face-to-face	0.30-0.42	0.15-0.53	—	—
	Teledermatology	0.79	0.72-0.93	—	—
Warshaw (34)	Face-to-face	0.56	0.53-0.60	0.76	0.73-0.79
	Teledermatology	0.43	0.39-0.47	0.59	0.56-0.63

Complete accuracy—accuracy based on the single most likely diagnosis. Partial accuracy—accuracy based on single most likely diagnosis and differential diagnosis. (From Whited JD. Summary of the Status of Teledermatology Research.¹⁰⁵)

In order to explore whether the differences in diagnostic agreement between teledermatologists and clinic-based dermatologists are significant, some studies have assessed the interobserver reliability between clinic-based dermatologists alone. Overall, these studies have yielded comparable results to those studies evaluating the interobserver reliability between teledermatologists and clinic-based dermatologists^{7,15,18}. For example, one study by Whited et al. found comparable rates of interobserver diagnostic reliability between clinic-based dermatologists (0.54-0.92), between clinic-based dermatologists and teledermatologists (0.41-0.95), and between teledermatologists (0.49-0.92).⁷

The intraobserver reliability using S&F and in-person dermatology consultation has been reported in a handful of studies and ranges from 0.31-0.95^{8-9,16,26-27}. Only two studies have reported intraobserver reliability using live interactive teledermatology, compared to in-clinic dermatology consultation, and their results ranged from 0.59-0.87.^{19,21}

It is notable to mention one study that explored a combined live interactive and S&F model of teledermatology. In this study, both interobserver and intraobserver reliability illustrated significant increases with this combined model compared to S&F alone.²⁸

STUDIES ON DIAGNOSTIC ACCURACY

The results from research studies evaluating the diagnostic accuracy of teledermatology are difficult to interpret given

that there is no single gold standard in the field of dermatology. Although a biopsy can be helpful in the establishment of many dermatologic diagnoses, it is mainly considered a gold standard for establishing a diagnosis of dermatologic malignancy. Other reference standards (e.g., KOH prep), can also be helpful in making a diagnosis. Studies that have reported on the diagnostic accuracy of teledermatology have confirmed diagnoses via biopsy (usually for neoplasms) or other validated reference standards.

Diagnostic accuracy rates have been reported at rates ranging from 0.30-0.97^{7,27,29-34} (Table 2-4). These rates are based on studies comparing S&F teledermatologists to clinic-based dermatologists. To date, there have been no studies that evaluate the diagnostic accuracy of live interactive teledermatology.

There have been four studies that have found comparable accuracy rates between teledermatologists and clinic-based dermatologists, and one study that found higher accuracy rates among teledermatologists compared to clinic-based dermatologists.^{7,27,31-33} In this study by Lozzi et al. teledermatologists were allowed to consult with each other as well as request additional information from clinic-based dermatologists.³³ One could argue that this study is actually more representative of a real-life scenario where teledermatologists would be allowed to consult others. A recent study by Warshaw et al. however, found poorer diagnostic accuracy rates among teledermatologists (aggregated diagnoses 59.5%, primary diagnoses 42.9%) compared to clinic-based dermatologists (aggregated

diagnoses 76.1%, primary diagnoses 56.3%) in the diagnosis of nonpigmented neoplasms.³⁴ A randomized-controlled trial comparing store and forward teledermatology with store and forward combined with live and interactive found that both modalities performed well as measured by diagnostic confidence, diagnostic concordance, and need for conventional consultation³⁵

STUDIES ON MANAGEMENT RELIABILITY

Overall, research studies assessing the reliability of management decisions made by teledermatologists compared to clinic-based dermatologists have been shown to be encouraging with management agreement ranging from 0.36-1.0.^{4,7,13,15,16,19,23,30,32,36-40} In one of the biggest studies which evaluated 129 patients and compared management plans between teledermatologists (using S&F) and clinic-based dermatologists, comparable reliability for both medical therapy and clinic-based therapy recommendations were found.⁷ Diagnostic testing recommendations, however, were not reliable. With regard to diagnostic testing, similar results were found in another study by Mahendran et al. in which 163 S&F referrals of patients with one lesion suspicious for skin cancer were evaluated.¹² This study found management reliability between the teledermatologist and the two clinic-based dermatology consultants to range from 52-55%.

There have, however, been some studies that have assessed the reliability of biopsy and operative recommendations, which have yielded positive results (agreement ranging from 0.76-1.0).^{30,32,36-38} For example, a study by Shapiro et al. which evaluated the skin growths in 49 patients by digital photographs and in clinic consultations found that the teledermatologist and clinic-based dermatologist recommended a biopsy in the same 26/49 patients (agreement of 1.0).³⁷ There was also a recent study, which used the consensus opinion of an expert panel as a reference standard in the assessment of management decisions.³⁴ This study found management plans between teledermatologists (S&F) and clinic-based dermatologists to be equivalent (78.8% versus 83.4% respectively).

There have not been many studies evaluating management reliability of live-interactive teledermatology. One study found interobserver agreement between clinic-based evaluations and teledermatologists for biopsy recommendations to be 86%.²³ Another study that evaluated agreement by categories of management plans between a teledermatologist and a clinic-based dermatologist found an agreement rate of 72%. (44/61 cases).¹⁹ The study by Edison et al. which evaluated both S&F and live interactive teledermatology, found that clinic-based dermatologists agreed with the management plans of S&F teledermatologists 66% of the time.²⁵ Clinic-based dermatologists agreed with live-interactive teledermatologists 75% of the time, and live-interactive teledermatologists agreed with S&F teledermatologists 64% of the time.

STUDIES ON OTHER PROCESS MEASURES

Other process measures that have been evaluated in teledermatology research studies include intermediate outcomes such as clinic visits avoided, time to initial contact with a dermatologist, time to intervention, and length of consult. With regard to these process measures, teledermatology has been shown to be superior to conventional care.^{1-2,8,10,15-16,31,38-39,41-58} Several studies have evaluated the number of teledermatology consults that obviated the need for a dermatology outpatient clinic visit. For S&F teledermatology the percent of clinic visits avoided ranges from 13-59%, while visits avoid with live-interactive teledermatology have been shown to range from 44.4-82%.^{8,10,12,15-16,31,41-47,50-53}

Time to initial contact with a dermatologist as well as time to intervention, which are both closely related to a patient's clinical course, has been shown to decrease with the use of teledermatology when compared to the conventional process of patient referral. A randomized-controlled trial by Whited et al. found that patients utilizing S&F teledermatology consultations reached a point of intervention significantly sooner than those patients undergoing the typical referral process (median 41 days versus 127 days, respectively).⁴³ Another study found similar results, illustrating that teledermatology referral patients on average were evaluated sooner than conventional referral (12 days versus 88 days, respectively).⁴⁴ A study evaluating the wait times of patients with suspected skin cancers to see a clinic-based dermatologist found that median wait times and time to treatment were shorter for both melanoma and squamous cell cancer patients referred by teledermatology.⁴⁸

With regard to the actual length of a consult, when compared to clinic-based visits, S&F teledermatology consults have been shown to take less time.¹⁻² A study by Whited et al. illustrated this point when it found that S&F teledermatologists needed an average time of 7.2 minutes to review a consult versus a conventional consult, which required 24.4 minutes.² Although live-interactive teledermatology has been shown to be similar to outpatient dermatology clinic visits with regard to length of consult, studies have shown that compared to clinic visits, live-interactive teledermatology visits lead to a decrease in overall time for the visit (waiting time, consult time, and travel time).⁵⁵⁻⁵⁷

Studies Examining Clinical Outcomes

Research studies evaluating the clinical outcomes associated with teledermatology, such as patient clinical course, are rare given the reasons stated above. Studies to date that have assessed such clinical outcomes, however, have been promising.

A randomized controlled trial by Pak et al. compared to the clinical courses of patients undergoing a dermatology consultation in the clinic versus S&F teledermatology.⁵⁸

Based on evaluations before and after 4 months, subjects were rated as “improved”, “no change”, and “worse”. 65% of patients in the clinic-based group and 64% of patients in the teledermatology-based group were rated as “improved”, illustrating comparable clinical courses. Another randomized controlled trial that assessed an online asynchronous tool for the delivery of follow-up care in patients with acne, found that the degree of improvement seen in those subjects using this online tool was equivalent to those receiving conventional clinic-based treatment.⁵⁹

There is one study that attempted to evaluate clinical improvement among patients undergoing live-interactive teledermatology consultations by retrospective review.⁶⁰ This study found that of the 127 patients reviewed, 58.3% were rated as illustrating “clinical improvement”.

Studies Examining Doctor/Patient Satisfaction

Patient satisfaction for both S&F and live-interactive teledermatology has been shown to be generally neutral, with some studies illustrating overall satisfaction ranging from 42-93%.^{1,15,19,24,61-69} A study by Collins et al. found that 38% of patients preferred clinic-based dermatology consultations, 32% preferred S&F teledermatology, and 30% were unsure.⁶⁵ Similarly, a study by Whited et al. found that 41.5% of patients preferred S&F teledermatology consultation, 36.5% preferred clinic-based consultation, and 22% felt neutral about either option.⁶⁶ One study evaluating patient satisfaction with live-interactive teledermatology found that 66% of patients reported teledermatology was as good as clinic-based care, while another study reported 59% believed live-interactive teledermatology and clinic-based consultations were equivalent in quality.^{19,68} In both of these studies, however, some patients (13% and 18%, respectively) did report some discomfort with using the camera during their interaction.

Studies assessing referring clinician satisfaction with S&F teledermatology have found overall satisfaction rates ranging from 21-92%.^{1,15,61-63,66,70-71} In some studies, referring physicians have expressed that they feel teledermatology provides them with some educational benefit.^{1,62} In a study by Collins et al. physicians communicated that they believed teledermatology improved access to clinical specialists.⁷⁰ In studies where S&F teledermatology was utilized, the main complaint elicited by referring physicians was the time requirement that was needed to generate a consult.^{15,61,63,70} Feedback was similar for studies evaluating referring physician satisfaction with live-interactive teledermatology.^{19,72}

Studies have shown that satisfaction of teledermatologists themselves is good overall.^{1,15,20,24,62,66} 70% of teledermatologists utilizing S&F to evaluate patients in a study by Pak et al. reported that they believed their consult was of sufficient quality to make a diagnosis.⁶² In another study by Whited et al. 100% of teledermatologists stated that S&F made triaging patients easier.⁶⁶ With regard to

the evaluation of live-interactive teledermatologists, one study found that 98% of teledermatologists believed they were able to establish a good rapport with the patient, while another study found that 80% of teledermatologists believed their examination was as thorough as it would have been in a clinic-based setting.^{20,24} The most common negative comment made by teledermatologists in these studies was that they did not feel as confident in their diagnosis as they would have in clinic.

Studies Examining Cost Effectiveness

Although few studies that evaluate the cost-effectiveness of S&F teledermatology exist, research to date has shown that this modality of teledermatology has the potential to be cost-effective, especially from a societal perspective which takes into account all aspects of cost (for example, loss of work, productivity, etc.) associated with an intervention.^{2,4,73,74} A study by Moreno-Ramerie et al. performed a cost-effectiveness analysis on patients that were being referred for a suspected skin cancer via S&F teledermatology.⁷³ The study found teledermatology to be more cost-effective than conventional care, with teledermatology costing less per patient (79.78 Euros versus 129.37 Euros) and leading to patients being seen much earlier than those referred as usual (12.3 days versus 88.6 days). Another study found that, although direct costs of teledermatology were slightly higher than conventional care (\$294 per patient for teledermatology versus \$283 per patient for conventional care), when lost productivity costs were taken into account, teledermatology resulted in cost savings (\$340 per patient for teledermatology versus \$372 per patient for conventional care).⁷⁴

There are many more studies that focus on the economic analysis of live-interactive teledermatology compared to S&F. Currently, the consensus is that live-interactive teledermatology tends to be more costly than conventional care.^{50,52,56,75-80} However, studies have shown that this generalization may not apply in all healthcare settings. For example, a study by Armstrong et al. found that operating costs for live-interactive teledermatology were actually less than the operating costs of an outpatient dermatology clinic (\$274/hour for teledermatology versus \$346/hour for in-person clinic) in a remote rural setting.⁷⁹ In addition to this, it is important to consider the fact that, although the cost of technology is currently considered to be a significant portion of the cost of teledermatology, as the integration of communications technology continues to become commonplace, the cost of technology will likely decrease considerably.

Secondary Applications of Teledermatology

With the ongoing improvement of communications technology, as well as its continued integration into society, the applications of teledermatology as a clinical tool are vast.

Research is now beginning to focus more on the utility of these applications, as they have the potential to address many of the problems related to poor access to dermatologic care.

Triage

As briefly mentioned above, teledermatology has the potential to play a significant role in patient triage. This is especially true for those patients with lesions suspicious for skin cancer, as wait times associated with conventional patient referral are often prolonged. Many research studies have shown that using teledermatology to triage cancer patients can decrease both their wait time and time to intervention.^{37,44,48,50} A study by Hsiao and Oh performed a chart review of patients who were treated for skin cancer as a result of conventional or teledermatology referral and found that the mean time intervals for initial consult (48 day versus 4 days, $p < .0001$), biopsy (57 days versus 38 days, $p = .034$), and surgery (125 days versus 104 days, $p = .006$) were all less in patients referred via teledermatology.⁵⁰ Yung et al. reported on the use of teledermoscopy as a triage tool noting that agreement between teledermoscopy and face-to-face dermatologists was high (87.7%). They concluded that teledermoscopy is an effective tool to help manage triage in an environment with long wait times for an appointment.⁸¹

Management of Chronic Skin Disease/ Follow-up Care

Patients with chronic skin diseases, such as psoriasis and acne, often seen in dermatology clinics on a more regular basis than other patients. The amount of follow-up care that is required for these patients makes teledermatology an interesting option to consider because it allows for the preservation of patient contact without the inconvenience of having patients come into clinic as regularly. Although there have been few studies to date, the utility of using teledermatologic tools for follow-up care in those patients requiring frequent monitoring is currently being explored. In a study by Binder et al. teledermatologic follow-up care was done via home-care nurses after an initial outpatient visit for a leg ulcer. At the end of this study, 71% of leg ulcers were noted to improve.⁸² As mentioned above, a recent randomized-controlled trial of acne patients found that there is value in utilizing teledermatology for follow-up care.⁵⁹ Watson et al. examined the utility of a tool allowing patients with acne to submit self-captured images and relevant history over a secure website, in lieu of a follow up office visit. Subjects had either four online, asynchronous follow up visit or four in-office follow-up visits. Patients and Doctors were pleased with the application and there was no difference in quality of care as measured by lesion counts.⁸³ (see Studies Examining **Clinical Outcomes**, acne RCT)

Education and Support for Physicians and Patients

The use of communications technology as a bridge to sharing educational information between healthcare providers and patients is an important aspect of teledermatology, as providing education ultimately affects the delivery of healthcare. The use of such tools has been used to train residents. In a study by Williams et al. internal medicine residents in a hospital where there was no dermatologist, received 12 months of dermatology training via videoconferencing.⁸⁴ After the dermatology training, residents illustrated an increase in knowledge scores, and over 85% reported that the lectures improved their ability to provide patient care. Digital images along with a patient history gathered during dermatology consultations have also been used as a teaching tool during dermatology residency training.⁸⁵

Because primary care physicians often manage dermatology patients, having access to educational tools that can help support their decision-making. In a study by Gerbert et al. primary care physicians were randomly assigned to an internet-based skin cancer triage tool.⁸⁶ The physicians who utilized this tool scored significantly higher than the control group in 9 out of 14 outcome measures, which included diagnosis and evaluation planning for several skin cancers. The use of communications technology (email, online forums, etc.) can also help to facilitate knowledge exchange between general practitioners and dermatologists, aiding with management decisions as well.

Given the ease with which one can gain access to communications technology, future applications of teledermatologic educational tools will likely integrate direct communication between the dermatologist and patient. Hofbauer et al. evaluated an internet-based question-answering service at a university hospital in Switzerland and found that of those patients who asked dermatology-related questions, many of them reported high rates of satisfaction and changed whether or not they visited a clinic based on online recommendations.⁸⁷ The internet can also serve as a place of support and education for some dermatology patients with chronic diseases. For example, a recent study examined the role of online support communities in patients with psoriasis and found that of those patients participating in this community, 41% reported improvement in their psoriasis, half reported in improvement in their quality of life, and 60% reported having better availability of social support.⁸⁸

Mobile Teledermatology

Mobile teledermatology refers to the use of mobile devices such as cellular phones and personal digital assistants (PDAs), to send or receive dermatologic patient information. Integrating these devices into dermatologic care would be feasible given their increasing popularity with

consumers, as well as their ability to transmit and receive information without needing a direct Internet connection. Such technology has the potential to play a role in areas such as remote patient monitoring and follow-up, triage, treatment adherence, and patient education. This is especially true given the recent improvement in the quality of cameras that are embedded in these devices. Although few studies exist that have evaluated diagnostic agreement between clinic-based consultations and teledermatology images sent from mobile devices, results have been positive with one study reporting a κ value of 0.94 for diagnostic concordance, and another reporting a concordance rate of 71%.^{89,16} One of these studies also asked patients for their feedback on mobile teledermatology and found that 60% were not worried about its possible uncertainty, 69% were convinced of its usability, and 53% were willing to pay to use a similar service in the future.¹⁶

The ability of cellular phones to transmit and receive SMS text messages is currently being investigated as a simple and cost-efficient tool for providing patient support and education. An article by Schreier et al. describes a cellular phone-based compliance management system for psoriasis patients currently under implementation.⁹⁰ With this system, patients are able to send data (photographs, adverse event reports, etc) to an online monitoring center and if necessary, dermatologists are able to provide feedback to patients via SMS text messages or email. The role of SMS text messages in improving adherence to medical treatment is currently being examined as well. A recent randomized-controlled trial in Boston, MA found that patients who received daily reminders to wear sunscreen via SMS text message had nearly double the rates of sunscreen use versus a control group.⁹¹

Teledermoscopy

Clinical tools, such as dermoscopy, are now being integrated into the capture of digital images. In fact, dermoscopy attachments for cameras are now commonly sold (Figure 2-1). The utility of dermoscopy is that it allows for direct microscopic examination of pigmented skin lesions. Capturing these images could impart value on the diagnostic reliability of teledermatology. One study found 91% concordance in diagnostic agreement between teledermatologists and clinic-based dermatologists, while another study reported a κ value ranging from 0.681-0.703 with regard to management recommendations for pigmented lesions.⁹²⁻⁹³ A pilot study by Ferrara et al. examined the diagnostic accuracy of teledermoscopic images of melanocytic neoplasms via histopathologic diagnosis and reported a rate of 83%.⁹⁴

Teledermatopathology

The incorporation of digital cameras into microscopes has allowed for the transmission of both static and real-time



FIGURE 2-1 Example of dermoscopy attachment for digital camera. Third Generation DermLite FOTO Digital Epiluminescence Microscopy System. (Image courtesy of 3Gen, LLC.)

dermatologic images. As a result, dermatopathologists are now able to offer their expert opinion to those in a geographic area where such a specialist may not be available. Studies have found concordance rates from 78-100% between teledermatopathologists examining static images versus conventional histopathologic diagnosis.⁹⁵⁻¹⁰⁰ A study by Morgan et al. evaluated real-time teledermatopathologic diagnoses and reported good agreement as well ($\kappa = 0.76$).¹⁰¹ Progress has been made in this field with the introduction of the virtual slide system (VSS) in 2007, which enables the creation of a high-resolution digitized image of a slide that allows it to be viewed at different magnifications. Results from a study evaluating use of the VSS on the diagnosis of inflammatory skin lesions, found that only 3 out of 4 cases were correctly diagnosed, which authors felt was less than optimal.¹⁰² Authors of the study did state, however, that continued training on the VSS would most likely lead to future improvements in the diagnostic utility of this tool.

ADOPTION CHALLENGES

Although the technology needed for the integration of teledermatology into clinical practices is readily available, several barriers impeding widespread adoption persist. (Figure 2-2) Many healthcare providers continue to exhibit reluctance towards the adoption of teledermatology. This reluctance may stem from a lack of sufficient randomized-clinical studies, or from providers feeling satisfied with the current status of their clinical practices. As mentioned earlier, healthcare providers are concerned that integrating teledermatologic tools into their practice could lead to an increase in workload. It is important to consider, however, that new models of teledermatology are moving toward

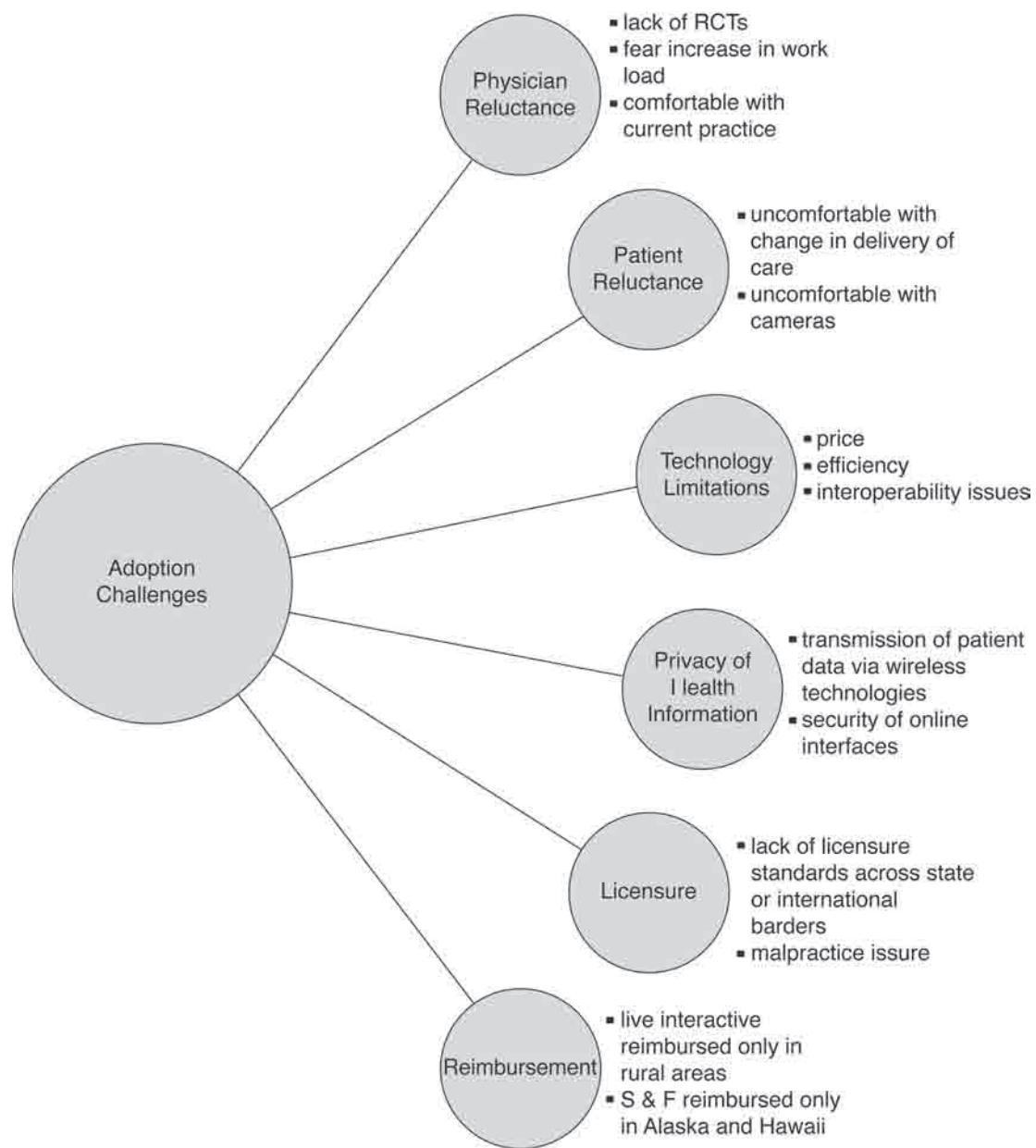


FIGURE 2-2 Challenges facing the adoption of teledermatology.

allowing for greater provider flexibility and versatility. Asynchronous models of teledermatology targeted at the most appropriate patients (e.g., those requiring frequent follow-up care) could allow for these patients to be seen more efficiently and at a time of convenience, allowing more time for dermatologists to see urgent patients in clinic.

Patients themselves may also feel reluctant to integrate teledermatology into their care. In previous studies, some patients have voiced feeling that “something was missing” during their teledermatology visit or that they were uncomfortable with the camera that was used.^{15,19,65,68} Emerging models of teledermatology, however, envision that teledermatologists will have some face-to-face contact with patients they are consulting (via live video

or previous clinic visit), making the experience more personal. As the integration of communications technology into clinical practices becomes more commonplace, we expect that teledermatology visits will feel more natural for patients. In addition, several studies have shown that there are a number of people who respond positively to teledermatology indicating that for some, adoption may be welcomed. (See section on *Studies Examining Doctor/Patient Satisfaction*)

Another challenge to the adoption of teledermatology lies in the technology itself. The price of utilized equipment is still considered significant in many situations, especially when high quality products are sought out. As previously mentioned, however, the rate at which technologic development is progressing is leading to greater affordability and

availability. The efficiency of current technology along with issues of interoperability between different devices remains a problem in some cases, but it is thought this will improve much over time.

Given the widespread use of wireless technologies to transmit patient data, especially with recent consumer-grade products that allow for patients to transmit their own clinical information, there have been growing concerns over the issues of privacy and security. Currently, several secure online interfaces are being created to help ensure that such healthcare information remain protected. The Health Information Portability and Accountability in the United States has set standards for the security of patient information.¹⁰² In addition, the Joint Commission on Accreditation of Healthcare Organizations also requires that high standards for the protection of patient information are met before granting accreditation to organizations.¹⁰³

Teledermatology allows a platform for the delivery of healthcare regardless of geographic boundaries. However, no licensure standards that have been created for the delivery of telemedical healthcare across state or international borders, creating a dilemma. Licensure in this scenario will be important to address in the future, given the issues that could arise with regard to malpractice. Clearly defining the responsibility of all parties involved with teledermatology consultations (referring physician, teledermatologists, etc.) is the key to avoiding future conflict.

Of all the challenges facing the adoption of teledermatology, reimbursement remains one of the biggest to be tackled. Currently Medicare and Medicaid reimburse physicians for live-interactive teledermatology consultations in only state-defined nonmetropolitan areas of the United States. S&F teledermatology consultations, however, are generally not reimbursed. This is true except in the states of Alaska and Hawaii, where Medicaid is currently funding S&F consultations on a trial basis because of the poor access to specialized care in these states.¹⁰⁵ The lack of randomized-controlled trials is a likely contributor to the reluctance of insurance companies to reimburse for teledermatology visits, which is a call to researchers in the field to continue with their efforts.

CONCLUSION

Research to date has illustrated the utility of teledermatology as a clinical tool and suggests that it is equivalent to face-to-face dermatologic care. Its applications, which include providing remote dermatologic care, aiding in patient triage, and providing a platform in which to educate patients and providers, are vast and valuable. Although there continue to be challenges facing the adoption of teledermatology into clinical practice, its integration is slowly becoming apparent. In 2003, American Telemedicine Association reported that more than 70 dermatology training programs were incorporating teledermatology into their practice,¹⁰⁶ and this number is likely rising.

The American Dermatology Association has released a statement with their position on the use of teledermatology, including guidelines for technology requirements, confidentiality standards, and licensure,¹⁰⁷ which is a sign that the value of teledermatology is recognized. With this in mind, however, it is acknowledged that much teledermatology research remains to be done. It is not until equivalence to conventional care is better elucidated that teledermatology will gain better acceptance in the medical community.

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Evidence-Based Patch Testing

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INTRODUCTION

Evidence-based medicine can be applied both to therapeutic interventions and diagnostic procedures. When applying evidence-based medicine to diagnosis, we referred to evidence-based diagnosis (EBD). EBD can contribute to the assessment of the validity, and accuracy, as well as possible adverse effects of any diagnostic procedure in relation to its costs. Therefore, practitioners could better serve those who are under their care by using evidence to determine best practices in diagnosing.

EVIDENCE-BASED DIAGNOSIS APPLIED TO PATCH TESTING

Patch testing is currently used in clinical practice as the most important investigative and diagnostic method available for studying delayed contact hypersensitivity. It is a relatively inexpensive and safe procedure designed to establish a causal link between sensitization to a specific agent and allergic contact dermatitis (ACD). Patch testing constitutes—together with a detailed clinical history and a complete physical examination—a crucial step in the diagnostic work-up of ACD. Properly interpreted, patch test reactions are acceptable as “scientific proof” of the cause of dermatitis and are of medicolegal importance. The procedure involves the epicutaneous application of a specific substance (allergen) that should induce a cutaneous inflammatory reaction in the susceptible (sensitized) person; whilst causing no reaction in a nonsensitized person. The local reaction, reproducing the dermatitis “in miniature”, provides a visible representation of the subject’s general ability to react to the substance. Patch testing may be considered as one the most direct of all methods of medical testing, because it employs the agent that causes the disease; it applies that agent to the target organ, and it reproduces locally the pathogenic and immunologic mechanisms and morphologic changes of the disease itself.

However, as a bioassay, patch testing still confronts several inherent methodologic problems and requires strict observation of the technical aspects and critical assessment of the results.

In this article, we will discuss the validity of patch testing in the context of the principles of EBD. We will also

address the considerations pertinent to the decision to perform patch testing in the individual specific patient.

WHEN AND WHY PATCH TESTING?

Patch testing is indicated when an allergic component of the dermatitis is suspected. It has been shown to be significant both, in confirming contact sensitivities suspected from the clinical history and in unveiling unsuspected sensitivities. A number of studies have shown that history and physical examination alone are insufficient to consistently evaluate a patient with ACD.^{1–3} Cronin¹ studied 1000 patients by thorough clinical investigation and patch testing and demonstrated that the accuracy of the clinical prediction varied, depending on the characteristics of the clinical dermatitis and the causative allergen. For nickel, the most frequent sensitizer in women, the allergy was anticipated in 64% of the subjects, whilst chromate, the most common sensitizer in men, was suspected only in 40% of the cases. For other common allergens such as lanolin and neomycin sensitization was predicted in only 16% and 8% of the cases respectively. Similarly, Fleming et al.² demonstrated that clinical questions were accurate to predict the causative allergen in only 29–54% of ACD cases, depending on the involved allergen. Reliable identification of causative allergens by history alone represents an overwhelming task in which we are usually unsuccessful. Podmore et al.³ patch tested 100 consecutive patients, 41 of them were tested for screening purposes (e.g. eczema without an obvious allergic contact factor or clinical contact dermatitis without an obvious allergen). In 59 patients, a contact allergen was strongly suspected. Diagnosis was confirmed in 32 patients. In addition, 17 patients had 23 unexpected positive reactions. At least 50% of the unexpected reactions were considered relevant to the patient’s skin condition. If only the clinically suspected substances are tested, then all other possible sensitivities—which are not immediately evident from the history—would be neglected. For this reason, a standard series of allergens should be applied in all patients with suspected contact dermatitis. In addition to the investigation of a probable ACD, patch testing should also be done to uncover unsuspected (“occult”) contact allergies in patients with chronic or nonresponsive eczematous dermatitis, especially those

with hand or hand-and-foot dermatitis (dyshidrotic, hyperkeratotic and even pustulosis palmaris et plantaris), stasis dermatitis, atopic dermatitis, nummular eczema, and unclassified eczema. Patch testing may also be considered in patients with eczematous psoriasis,⁴ essential pruritus and suspected drug eruptions.⁵ Finally, it may be indicated when dealing with any dermatitis that persists for more than 3 months, is resistant to an appropriate therapy, or worsens during topical treatment. When these patients are assessed clinically but without patch testing, they may not be suspected of having an allergic component. Moreover, in many cases, the offending agent is present in the topical products prescribed or self-administered for the treatment of the primary disease. However, when testing these patients, bear in mind that, as the prevalence of allergic contact dermatitis is deemed to be lower than in patients meeting the case definition of allergic contact dermatitis,⁶ the predictive value of patch testing will decline (see the following).

Although patch-testing is primarily conducted according to the clinical history and physical examination, the diagnostic process is bi-directional and test results will guide further questioning and investigation. Reconsidering the history in the light of the test results can lead to recognition of many concealed sources of causative exposure. Even when uncovering unsuspected contact allergies are important, the significance of these sensitivities to the clinical dermatitis varies substantially. Many times, no clinical relevance is found, whilst other times, avoiding exposure to the sensitizer may constitute the only measure that can be adopted to control the flares in a chronic, recalcitrant dermatitis. The correct diagnosis and characterization of the causative agent(s) of the patient's dermatitis constitute essential prerequisites for adequate therapeutic and preventive measures to be established. Conversely, without the use of diagnostic patch testing, the patient may be given needless prohibitions in a vain attempt to improve the dermatitis.

WHAT IS THE VALIDITY OF PATCH TESTING RESULTS?

The validity (credibility, believability) of any test system is its intrinsic ability to detect or measure the aimed biologic phenomenon, (i.e., to determine which individuals have the target disease and which do not), relying on the test capability to detect both true-positive and true-negative reactions, while minimizing the number of false-positive and false-negative reactions. In the case of patch testing; does a positive patch test reaction predict contact sensitization with certainty or it can be elicited by a different biologic phenomenon like contact irritancy? A single patch test is a 'snapshot' of the tempo of an evolving immunologic process, and the issue of whether a positive patch test reaction is causally linked to the disease being studied involves several pitfalls including the inherent risk of

false-positive responses, mostly because of irritancy, and the difficulties in assessing clinical relevance. Besides, the magnitude of the problem of false-negative results is largely unknown.

The Problem of False-Positive and False-Negative Patch Test Reactions

The ideal patch test should correctly diagnose contact sensitization while producing no false-positive or false-negative reactions. However, even when an appropriate testing technique is applied, false-negative and false-positive reactions may occur. The frequency of false-negative reactions is difficult to evaluate. A false-negative reaction can occur for a number of reasons: (1) failure to perform delayed readings after allergen removal and evaluation at 48 hours, which is especially important for allergens known to elicit delayed reactions, and when testing elderly patients, who may present a protracted immunologic response; (2) the test concentration and/or the amount of the substance applied may have been insufficient; (3) the vehicle may not have released a sufficient amount of the allergen (the biologic availability was too low); (4) the patient skin is unresponsive by prior sun exposure, local application of corticosteroids, systemic administration of corticosteroids or immunosuppressors or other causes of skin hyporeactivity (5) the test site might have been inappropriate; (6) the occlusion might have been insufficient; (7) there was an inadequate replication by the test of the real exposure conditions, namely irritation, occlusion, heat, mechanical trauma, etc, that might enhance the percutaneous penetration of the allergens and cannot be reproduced in patch testing.

When patch testing with a particular substance is negative in a patient who has an evident dermatitis from contact with that substance, the putative allergen should be retested—perhaps in a different concentration, with a different vehicle, or with a different testing method, such as open or semi-open tests and use tests and/or repeated open application test (ROAT). Likewise, the investigator must be aware of the pitfalls of false-positive reactions. A false-positive reaction may be attributed to several causes, such as: (1) testing with allergens that are marginally irritants, (e.g., metals, formaldehyde, epoxy resin, etc.); (2) testing with allergens at concentrations that exceed their irritancy thresholds; (3) spill over reaction from a nearby true-positive reaction; (4) multiple simultaneous positive reactions; (5) testing patients with active dermatitis or otherwise sensible or irritable skin. Certainly, these lists are not exhaustive. The issues of skin hyper and/or hyporeactivity would be better assessed if appropriate negative and positive controls were routinely applied in clinical patch testing. The negative control would be a chamber containing only petrolatum, whilst the positive control should be a mild irritant such as 75% aqueous propylene glycol, 20% nonanoic acid, or 0.25%

sodium lauryl sulphate. To discriminate between false-positive reactions and true allergic reactions, we can repeat patch testing of the individual allergen with lower concentrations or serial dilutions, repeat patch testing with 24 hours occlusion, or perform additional tests such as the ROAT.^{7,8} Irritation reactions in ROAT are very limited compared to patch tests.

Even if the allergic nature of a positive reaction as read by international guidelines cannot be taken for granted, for most common allergens a positive patch-test reaction is predictive for contact sensitization.⁹ The validity of patch testing may, therefore, be considered as good for many allergens, if tested under controlled conditions and in the proper concentration, and patch testing is performed and evaluated according to the international guidelines.¹⁰

WHAT ARE THE INDICATORS FOR EVALUATING THE VALIDITY OF A DIAGNOSTIC TEST?

The statistical principles that underlie the evaluation of diagnostic tests are frequently overlooked by clinicians. These principles are substantial in recognizing the inherent limitations that are present when applying diagnostic tests. The classic indicators for evaluating the accuracy of diagnostic tests are the sensitivity, the specificity, the predictive value (PV) and the likelihood ratios (LR). These indicators compare the diagnostic discrimination of the test to the reference criterion or gold standard, which, by definition, has a sensitivity and a specificity of 100%. The concept can be delineated using a 2×2 contingency table that takes into account the test result (i.e., interpreted as positive or negative) and the presence or absence of the disease being studied (Table 3-1).

CONTACT ALLERGY			
Patch Test Result	Present	Absent	Predictive Value
Positive	True Positive (TP)	False Positive (FP)	Positive (TP / TP + FP)
Negative	False Negative (FN)	True Negative (TN)	Negative (TN / TN + FN)
SENSITIVITY (TP / TP + FN)		SPECIFICITY (TN / TN + FP)	

Sensitivity = $TP / (TP + FN)$, specificity = $TN / (FP + TN)$

Positive predictive value = $TP / (TP + FP)$, negative predictive value = $TN / (FN + TN)$

Positive likelihood ratio (LHR+) = sensitivity / (1 - specificity)

Negative likelihood ratio (LHR-) = $(1 - \text{sensitivity}) / \text{specificity}$

Prevalence = $(TP + FN) / (TP + FP + FN + TN)$

Pretest odds = prevalence / (1 - prevalence), post-test odds = pretest odds \times likelihood ratio;

Post-test probability = post-test odds / (post-test odds + 1)

Sensitivity and Specificity

The key to patch testing is to allocate the tested subjects into either those who are allergic to the test chemical and should have a positive result or those who are not allergic, who should have a negative result. As has been stated before, those instances in which the test result is positive, but no disease is present, are called false-positive results. The negative test results found when disease was actually present are called false-negative results. The proportion of subjects with a positive test result, out of all those with disease is known as the sensitivity of the test. In our scenario, it measures the proportion of allergic individuals that are correctly identified by the test; ergo, it measures how sensitive the test is to detect contact allergy. Specificity is the proportion of subjects with an appropriate negative test result out of all those without disease. In other words, sensitivity and specificity indicate the proportion of individuals that have been correctly identified as allergic or not allergic.

These indices are the most commonly reported measures of test efficacy, provide stable estimates of the test's diagnostic discrimination and can be applied to any diagnostic test irrespective of the characteristics of the population on which the test is used.^{8,9,11–13}

Predictive Values

Although the concepts of sensitivity and specificity are required to determine the validity and accuracy of a diagnostic test, from a clinical point of view it is more important to determine to what extent the test can help estimate the probability of presence or absence of disease after testing. In other words, in clinical practice it is essential to know how a particular test result predicts the risk of disease. Sensitivities and specificities do not do this: they describe how abnormality (or normality) predicts particular test results. Physicians need to make inferences about the presence or absence of disease from an obtained test result. There are two ways to quantify this inference: predictive values and likelihood ratios.¹⁴ The traditional concept of predictive values (Table 3-1) presents the absolute probability that the disease is present (positive predictive value) or absent (negative predictive value). The positive predictive value of the test (PV+) is measured as the percentage of true-positive results out of all the positive test results. It is an estimate of the probability that a patient with a positive test result actually has the disease. Similarly, the percentage of true-negative results out of all the negative test results is referred to as the negative predictive value of the test (PV-). The positive and negative predictive values are of great importance for clinicians, who interpret the test results in a case by case basis and may be applied in clinical decision-making. However, these values are influenced not only by the sensitivity and specificity of the test, but also by the

prevalence of the disease in the population upon which the test is applied.^{14,15} If the rate of disease in the population tested is low, then the PV- increases and the PV+ decreases. In general, when the prevalence of the specified disease is low, even a test with high specificity will produce a large number of false positives, thereby reducing the PV+ of the test.¹⁶ Thus, the PV will vary depending not only on the test's properties but also on the prevalence of the disease in the population upon which the test is applied. Therefore, they do not offer a single measure to describe the test's inherent accuracy.

Likelihood Ratios

As PVs depend on the prevalence of the disease, they can rarely be generalized beyond the study (except when the study is based on a suitable random sample, as is sometimes the case for population screening studies). To overcome the difficulty arising from interpretation of PVs, decision analysts have proposed an alternative method to assess the predictive properties of a test: the likelihood ratio (LHR).^{14,17,18} LHRs are alternative statistics for summarizing diagnostic accuracy, which have several particularly powerful properties that make them more useful clinically than other statistics. Conceptually the LHR is the ratio of two probabilities, namely the probability that a specific test result is obtained in patients with the disease, divided by the probability of obtaining the same test result in patients without the disease. In the case of dichotomous test measures, the likelihood ratios have a direct relationship to sensitivity and specificity that can be summarized as follows: Positive likelihood ratio (LHR+) = sensitivity/(1 – specificity); Negative likelihood ratio (LHR-) = (1 – sensitivity)/specificity. However, unlike sensitivity and specificity, computation of the LHR does not require dichotomization of test results. Forcing dichotomization on multicategory test results may discard useful diagnostic information.¹⁹ An LHR greater than 1 indicates that the test result is associated with the presence of the disease, whereas an LHR less than 1 indicates that the test result is associated with the absence of disease. An LHR of 1 implies that the test result is equally likely to occur among patients with the disease as in patients without the disease. The further LHR are from 1 the stronger the evidence for the presence or absence of disease. LHR above 10 and below 0.1 are considered to provide strong evidence to rule in or rule out diagnoses respectively in most circumstances. LHR+ from 5 to 10 and LHR- from 0.1 to 0.2 provide moderate evidence for the presence or absence of disease. Tests with LHRs ranging from 0.33 to 3 rarely alter clinical decisions. LHR are ratios of probabilities, and can be treated in the same way as risk ratios for the purposes of calculating confidence intervals.^{12,19} Theoretically, LHRs (unlike predictive values) are independent from the prevalence of the disease. Actually, LHRs may differ across various clinical settings and may be affected by the same limitations discussed above.

Diagnostic Odds Ratio, Pre-test and Post-test Odds, Pre-test and Post-test Probabilities

An alternative way to compare tests is by means of the diagnostic odds ratio. The diagnostic odds ratio is calculated as $(\text{sensitivity} \times \text{specificity}) / [(1 - \text{sensitivity}) \times (1 - \text{specificity})]$ or as LHR+ divided by LHR-.²⁰ Potentially useful tests tend to have diagnostic odds ratios well above 20 (e.g., a LHR+ of 7 and a LHR- of less than 0.3). Other indicators that can help estimate the probability of disease after testing are the pretest and post-test odds and pre-test and post-test probability (Table 3-1). The sensitivity and specificity of a diagnostic test and the pre-test probability of disease can be used to estimate the post-test probability in an individual patient. Without any additional information, pre-test probability equals the prevalence of a disorder. If more information becomes available from clinical history, physical examination, clinical investigations, and diagnostic tests, then the probability of having or not having a disease will increase and even come close to 100%. The post-test odds are defined as the pre-test odds multiplied by the LHR+ of a test. The resulting post-test odds can be converted to a post-test probability of disease that is identical to the predictive value of the test. An estimate of the post-test probability of disease that is more relevant for an individual patient can be obtained by adjusting the pretest probability, taking into account patient characteristics and clinical experience.

WHAT ARE THE PROBLEMS WITH THE INDICATORS OF TEST VALIDITY WHEN APPLIED TO CLINICAL PATCH TESTING?

When we want to determine the accuracy of a diagnostic test using measures such as sensitivity, specificity, or PV, we should know in advance which subjects have the disease and are being studied based on some gold standard criterion. The optimal design for assessing the accuracy of a diagnostic test is considered to be a prospective blind comparison of the test, and a reference test or gold standard in a consecutive series of patients from a relevant clinical population.²⁰ As patch testing constitutes the only reliable and readily available test for diagnosis of contact allergy, the gold standard for comparison must be a confident clinical diagnosis made through the exhaustive study of each case and fulfillment of a precise case definition, in terms of the clinical findings, history of exposure to the tested substance, and reproducibility of the response with an appropriate time course after exposure.⁶ Alternatively, a repeated open application test (ROAT) or a controlled exposure to the tested substance can be envisaged as a reference for comparison. However, these tests also have a certain degree of ambiguity and need further standardization.²¹ Available data concerning validity and accuracy of

patch testing as a diagnostic tool are quite limited because, in clinical grounds, we usually do not apply diagnostic tests to groups of subjects who are known to have the disease we are trying to diagnose, (i.e., with incontrovertible contact sensitivity to the substances being tested). Similarly, data regarding testing in subjects without contact dermatitis are scarce.

To assess the validity of patch test screening trays in the evaluation of patients with allergic contact dermatitis, Nethercott and Holness²² tested 1032 patients, 639 of them with the International Contact Dermatitis Research Group (ICDRG) standard series and 393 with the North American Contact Dermatitis Group (NACDG) standard series, with the use of Al-Test patches or Finn Chambers. They found that sensitivity, specificity, positive accuracy, negative accuracy and validity index for the ICDRG and NACDG screening series were 0.68, 0.77, 0.66, 0.79, 0.72 and 0.77, 0.71, 0.66, 0.79, 0.74, respectively. Applying Nethercott's estimates for sensitivity and specificity, we can calculate the LHR+: sensitivity/(1 - specificity) = 0.68/(1 - 0.77) = 2.95, and the LHR:(1 - sensitivity)/specificity = (1 - 0.68)/0.77 = 0.43. These values are far from being ideal as nearly 30% of all patch test results were considered inaccurate. Note, however, that the authors considered those patients with positive test results in which investigation did not provide evidence to support clinical relevance (either present or past) as having false-positive tests. Similarly, patients with negative test results to the screening series in which further testing revealed positive responses to other allergens were taken to have false-negative screening tests.

Other important consideration concerning the validity of clinical patch testing is that patch testing does not represent a particular test –such as serum glucose-, but rather a technique of testing. Thus, sensitivity, specificity, PV or LHR data may be allergen specific and will vary depending on the allergens tested and also according to the degree of severity of the patch-test reaction. Thus, we have to keep in mind that the accuracy of clinical patch testing may be higher for one allergen than for another, and also, higher in ++ and +++ reactions versus + reactions. In addition, not only the allergen but also the allergen concentration has to be considered when assessing patch test validity. Delayed sensitivity is a dose-related phenomenon and the outcome of an individual patch test not only depends on the existence of delayed hypersensitivity to the tested allergen but also on the allergen concentration and the delivered dose. Therefore, the test concentration has an essential role in determining the amount of positive test results to be obtained. The allergen dose should be kept sufficiently high to detect allergy in weakly sensitized individuals but low enough to minimize irritant reactions and the risk of sensitizing the patient. When a test substance has low irritant properties, it is possible to use a relatively high test concentration, hence allergic reactions will be more likely elicited. Conversely, if the substance has a fairly high irritant potential, then a lower test concentration will have to be used

to avoid the induction of false-positive irritant reactions. In the latter circumstance, allergic reactions are less likely elicited, especially in weakly sensitized persons. Variations in the cutoff concentrations will determine changes in the balance between positive and negative results. If the allergen concentration is raised, both true-positive and false-positive test results will increase and the number of false-negatives will decrease; the sensitivity increases and specificity decreases. Conversely, if the allergen concentration is reduced, we will have less false-positive test results, but also more false-negative responses. The specificity increases but sensitivity will decline. Therefore, the sensitivity and specificity of the test, as well as the predictive values are related to the elicitation concentration of the allergen. The choice of allergen dose is a compromise; it should maximize the chance of obtaining true-positive results, while minimizing the number of false-positive irritant results in nonallergic subjects. Patch test concentrations for most allergens, even for allergens in the recommended standard screening series, have been established testing groups of patients supposed to have allergic contact dermatitis. In this context, a concentration is considered appropriate when capable of eliciting a reasonable proportion of true-positive tests results, (i.e., positive results that were considered relevant on clinical grounds), whilst eliciting a reasonably low proportion of irritant results according to morphologic criteria. However, the threshold for irritancy shows huge variance among individuals, and there are large interindividual variations in the minimal amount of allergen required to elicit an allergic reaction. So, allergen concentrations would be better estimated employing serial dilution test technique on patients proved to be sensitive to the tested allergen through controlled exposure, and also, on nonsensitive controls. Using this technique it would be possible to establish the concentrations eliciting strong, optimal, and minimal reactions. Thus, the mean, standard error and ranges of reactivity for the different allergens could be calculated. This procedure has been used to standardize some patch testing materials such as TRUE TestTM.²³ The cutoff concentration for TRUE Test allergens was determined as the minimum concentration that caused a 2+ reaction in at least 90% of sensitive patients.²³ On the other hand, comparative multicenter studies with TRUE Test and Finn chamber technique indicate proximity in limits of weak sensitization and irritancy for several standard allergens, such as nickel, dichromate, cobalt, balsam of Peru, fragrance mix, carba mix and thimerosal.²⁴

Finally, in clinical patch testing, positive reactions are at least ten times less frequent than negative ones. Therefore, even assuming that the test has high specificity, false-positive reactions will have great impact on the proportion of true positives out of all positives elicited (i.e., the PV+ of the test). This substantiates the importance of achieving a high prevalence rate of truly sensitized patients through a careful clinical assessment before patch testing. When the rate of allergic persons tested increases (i.e., patch testing is

used mostly to confirm a clinical diagnosis of ACD), then the PV+ will increase at the same test sensitivity.¹³

WHAT ARE THE ADDITIONAL PROBLEMS THAT MAY AFFECT THE VALIDITY OF CLINICAL PATCH TESTING?

There are several sources of unreliability that are inherent to clinical patch testing and that may interfere with the reliability of the results. Recognizing the benefits of patch testing, as well as all its possible pitfalls is of utmost importance to the physician using this method for clinical diagnosis.

Problems associated with the Patch Test Methodology

Standardization of the patch test technique is essential for reproducible results. Significant research on chemical and toxicologic aspects of test allergens, appropriate vehicles, and skin penetration, all contributed to the development of reliable and consistent patch test techniques. Yet, systematic studies for several important aspects are still lacking, and patch testing still confronts inherent methodologic problems. Several factors may influence patch test reactions and many sources of unreliability still exist, including variations in patch test materials, technique and methodology, as well as inherent biologic variability of patch test responses. Technical inconsistencies, such as variations in the amount of material applied can lead to erroneous results. The ideal test situation is a test area completely covered with the test preparation without any spreading outside that area. Excessive amounts can provoke spillover and irritant reactions, whilst inadequate dosing may, conversely, result in false-negative and doubtful reactions. The amount of allergen applied with the Finn Chamber technique should approximate to 20 mg, but, as a manually dispensed system, the amount of allergen applied is potentially variable depending on technique.²⁵ Other factors, such as the patch test system used may induce variability. The degree of occlusion and the conformity to the skin surface are different with the different systems and could be responsible for differences on the kinetics of allergen penetration. Also, the use of an appropriate vehicle is crucial as it influences the bioavailability and subsequent percutaneous penetration of the allergen. Petrolatum remains the standard vehicle for most allergens, with the exception of the TRUE Test. Earlier studies demonstrated that patch test suspensions in petrolatum contained undispersed allergen particles, and both the particle size and number differed significantly between different test substances and different manufacturers.^{26,27} This was frequently seen with metal salts, such as nickel sulphate,²⁸ but other test substances, such as disperse dyes²⁹ also produced a number of problems. The nonhomogeneous release of allergen from the vehicle may result in false-positive reactions.²⁸

Furthermore, many studies have found poor stability for some allergens.³⁰ Allergenic degradation products can be formed during storage, mostly by oxidation, as in the case of terpenes, such as limonene and linalool. In these circumstances, it may be difficult to determine the real allergenic fraction. In addition, much research is needed to define the chemical structure and to characterize the allergenic fractions of some complex allergenic substances such as balsam of Peru, colophony, or wool alcohols.

Problems associated with the applied amount of allergen, the stability and the vehicle seems to be solved with the “ready to use” delivery systems, such as TRUE Test, which has been pharmaceutically optimized concerning stability, solubility, and bioavailability of the allergens. However, only the standard series and a few additional allergens are available with TRUE Test.

The methodologic inconsistencies in patch testing may have several implications, including inappropriate diagnosis and incorrect counseling for the individual patient, as well as unfeasibility in the comparison of patch test results from different departments. Advances are being made in the optimization of patch test preparations and the dispersion of allergens and the quality of these materials has significantly improved in the last 15 years, but much work is still needed.

Validity of Testing with the Standard Series of Allergens

Most clinical cases of ACD are caused by a relatively small number of chemicals. Because of this, patients are tested with a group of 20 to 25 relevant test preparations consisting of chemically defined compounds, mixes of allergens, and natural and synthetic compounds found in the industrial and domestic settings grouped in a “standard series” as a primary screening procedure for suspected ACD patients. These series have been recommended by research groups such as the ICDRG³¹ the European and Environmental Contact Dermatitis Research Group (EECDRG),³² and the NACDG,³³ with minor changes in the different countries because of regional differences in exposure to sensitizing compounds. Their constitution is based on statistic of allergens and they are periodically revised to adapt to changes in exposure, introduction of new environmental allergens onto the market, and information regarding irritation, active sensitization, etc. Requirements to include a chemical in a standard series have been formulated by Bruze et al.³⁴ Demands on a sensitizer in the standard series are: being common in the environment; contact allergy rate above 0.5-1.0% in routinely tested CD patients; reliable patch test results, high degree of clinical relevance and minimal adverse effects, particularly patch test sensitization. When testing with these substances, it is reasonable to assume that most of the obtained positive reactions can be ascribed to contact allergy. The usefulness of this screening series has been confirmed, even when the percentage

of sensitivities detected by the standard series is variable in the different studies.^{33,35-38} In a multicenter study in 4824 consecutive patients from five European contact dermatitis departments, the sensitivities detected by the standard series alone ranged from 37 to 73% depending on the testing institution.³⁵ Patients with positive reactions only to additional allergens and negative to the standard series varied in frequency from 5 to 23% between the different centers. Sherertz and Swartz³⁶ found that 76% (499) of their patients had positive patch tests; 36% (179) of positive reactions occurred to allergens in the standard series exclusively; 24% (122) were positive only to additional allergens and negative to the standard series, and 40% (198) reacted both to the standard series and additional allergens. The authors concluded that the standard series is a useful screening tool, since of all patients who had positive reactions, 75% would have been diagnosed as having contact allergy if the standard series alone had been used. However, testing with additional allergens is also important given that more than half of these patients had at least one additional contact sensitivity that would not have been detected if supplemental allergens had not been used. Cohen et al.³³ tested 732 consecutive patients with the NACDG standard 20 allergens, the NACDG extended series and other allergens if estimated necessary. Overall, 363 patients (50%) had positive patch test reactions. Of these; 23% had positive reactions to the standard series of 20 allergens alone, 40% had positive reactions only to allergens in the supplementary group and 37% had a positive reaction to a standard series allergen and an additional supplementary allergen. Of the total cohort of 363 reactors, 221 patients (61%) were considered to have clinically relevant positive patch test reactions. Only patients with current clinical relevance were included in this group. Those patients reacting only to a standard series allergen had a high rate of clinical relevance (69%). However, they accounted for only 15.7% of patients with current clinically relevant reactions. The remaining 74% of clinically relevant reactions were detected only with the use of supplementary allergens alone or in conjunction with the standard series. The authors concluded that the screening patch testing should be done with an extended series of allergens including many from the supplementary series. Therefore, the NACDG developed an extended screening series containing more than twice the number of allergens than the original standard series.³⁷ In a multicenter study from the Informational Network of Dermatological Clinics (IVDK) in Germany,³⁸ 4140 patients were tested with the German Standard Series. Contact sensitization was diagnosed in 47% of patients tested, varying between 30 to 64% in the different centers. Forty percent of all patients proven to have contact allergy, were diagnosed using the standard series alone, whilst 20% of cases were diagnosed solely with additional allergens (occupation-specific or material brought in by the patient). Veien et al.³⁹ tested 6759 patients with the European standard series over a 5-year

period. Additional allergens were tested in 1450 of these patients. Positive reactions to the allergens in the standard series were seen in 1941 patients (29%), whilst 236 of the 1450 patients (16%) also tested with substances not included in the standard series had one or more positive reactions. Of the 1941 patients with positive patch tests, 1705 (88%) reacted only to substances in the standard series, 98 patients (5%) reacted both to substances in the standard series and to additional non-standard substances, while 138 (7%) reacted only to nonstandard substances. Therefore, most studies underline the importance of testing with the standard series, adding when necessary supplementary allergens from the complementary "aimed" trays, according to the clinical circumstance. The variations observed by the different authors may be attributed to differences in the population tested, (i.e. differences in exposure, in the number of additional substances tested, etc.) The absolute frequency of contact allergy in any population will never be known, but the more substances and products are tested, the greater will be the observed percentage of sensitization.

Validity of testing with other Nonstandardized Allergens

Most patients should be tested to a standard series, additional series or individual allergens will be selected depending on the history and the distribution of the dermatitis, the occupation and the geographic area. The characterization of a patch test allergen requires an adequate knowledge of its sensitizing capacity, its occurrence in the environment and, if possible, the results of testing of a large number of subjects. Most allergens from the standard tray and the most commonly used additional "aimed" trays are chemically defined materials of high purity and a large amount of clinical data has been accumulated concerning patch testing concentrations. When testing with these substances, it is reasonable to assume that most of the obtained positive reactions have significance and that investigation to assess relevance is warranted. In contrast, testing with nonstandard allergens, should be undertaken with caution. These may be chemically pure substances, but often they are compound products and may contain unknown components. Moreover, some components can be irritants; such is the case for many industrial products. Specialized textbooks regarding test's concentrations for many nonstandardized materials are currently available.⁴⁰ This information is of practical value as a starting point when testing with these materials. However, remember that for several of these substances, there has been little research concerning test concentrations and suitable vehicles. When testing chemicals for which there are limited data, we have to determine the appropriate strategy of testing and the valid test concentration, as we lack the information to categorically substantiate any conclusion. Therefore, patch testing with those materials may have little to contribute

diagnostically unless there is a definite clinical suggestion of their responsibility in the causation of the dermatitis. Finally, there are substances for which no information exists, except the chemical composition provided through the Material Safety Data Sheets for industrial products or the list of ingredients for household, cosmetic and toiletry products. Usually these products are technical grade chemicals; therefore, it should always be considered that they may contain unknown components. Should any substance be considered potentially irritant, an open use test may be envisaged. It should be performed with diluted substances, whose concentration can be progressively increased as far as no response either allergic or irritant appears. It is often helpful to patch test an uncommon substance at two or three tenfold serial dilution, such as 0.01% 0.1% and 1.0%. This procedure will prevent serious irritant reactions and may help to distinguish between irritant and allergic reactions.⁴¹ If an allergen is serially diluted, we usually observe a gradual reduction in the intensity of an allergic reaction, whilst an irritant reaction will tend to disappear abruptly. A gradually declining reaction, still distinctly positive at 0.01% or even 0.001%, constitutes highly suggestive evidence of contact allergy to the tested substance. It has been the usual practice to determine the "safe" or "nonirritating" test concentration for new materials, by testing in control groups. However, before any human test is performed, complete toxicologic information of the material must be procured. In addition, the control subjects should be followed up for 1 month to rule out active sensitization. It is recommended to test at least 20 control subjects based on the premise that if none reacts at the selected concentration, then, the testing is above the 95% one-tailed confidence limit. Usually, the test is performed with several concentrations, selecting the highest nonirritant concentration as the elicitation (cutoff) concentration. The highest nonirritant concentration is then applied to the subject with suspect ACD to the substance. The development of a positive patch test response with the morphologic attributes of an allergic reaction will constitute evidence of contact sensitization because of the substance.

The validity of patch testing may, therefore, be considered as good for standard allergens and allergens from many of the additional series, if tested under controlled conditions and in the proper concentration, but may be considered as poor for poorly standardized substances or for substances with unknown skin irritant potential.

Problems Derived From Testing With Allergen Series (multi-testing)

When testing with allergen series, we are, in fact, performing several individual tests with different allergens. If the cutoff concentration for each individual allergen in the series were settled at a 95% upper confidence limit, then, from a statistical viewpoint, each time we test 20 substances

in a nonsensitized person, there would be a 100% chance of eliciting a false-positive result from one of the substances tested. If we set the upper confidence interval at 99%, (i.e., assuming a false-positive response rate of 1% for each substance), we still have a 20% possibility of eliciting a false-positive result each time we test 20 substances.^{11,13} As we consider the tray of substances as a single screening test, rather than an assemblage of individual substances, we are dealing with a confidence interval of 80%, well below the conventional 95% confidence interval used in other diagnostic tests. If we wish to use a 95% confidence interval for patch-test screening and reduce the number of false positive reactions, it would be necessary to lower the cutoff concentration of the individual test substances, which will simultaneously reduce the true-positive response rate. Alternatively, we can consider reducing the number of test substances in the standard screening series to the indispensable minimum to diminish the risk of false-positive reactions. The above-mentioned concepts stress the significance of carefully assessing the clinical relevance of all positive reactions. Diepgen and Coenraads¹³ delineated another problem associated with testing multiple substances. When estimating differences in sensitization rates between two groups of subjects (e.g., between males and females or between atopics and nonatopics), we frequently perform pairwise comparisons using chi-square tests, one for each allergen tested, setting a *p*-value of 0.05 as statistically significant. In this circumstance, and for a series of only ten allergens, there is a random possibility of over 40% of finding by chance a statistically significant difference for at least one allergen between the two groups.

Problems Derived From the Reading and the Interpretation of Patch Test Reactions

Even when the proposals of the ICDRG in 1970¹⁰ standardizing the patch test readings were generally accepted and represented a substantial advance, reading of patch test responses needs to be considered eminently subjective and constitute one of the limitations of the method. Patch testing is a perceptual test, based on inspection and palpation of the test area. As any test that involves human perception and judgment, patch testing is bedeviled by variability of reporting on results. Especially, the reader's background knowledge and experience have great importance in the validity of the reported patch results. In epidemiologic studies, this variability is recognized as an inevitable consequence of the use of perceptual tests.

The classification and score grading of patch test reactions depend on descriptive morphology. The significant point in assessing a positive patch test is ascertaining whether it represents an allergic reaction or a false-positive reaction. Typical morphologic features of a positive allergic patch test reaction are erythema, edema, papules, and vesicles (or bullae). At least an erythematous infiltration and/or

papules should be present for a reaction to be considered allergic, whilst reactions that show only erythema without infiltration, called doubtful reactions, are frequently nonspecific or correspond to irritancy. Allergic patch test reactions are traditionally scored in terms of intensity, and a grading scale from 1+ to 3+ is currently accepted for ranking these allergic reactions.¹⁰ However, even when all reading systems are based on the same morphologic features, it remains some variation in the exact definition of the different grades of this scale between the different working groups. For instance, there are discrepancies in the reading of the 1+ reaction. Some groups define the 1+ reaction as homogeneous redness in the whole test area with scattered papules, whilst others only require redness and homogeneous infiltration in the whole test area. No real consensus has been reached in this matter so far.

Such minor differences of categorization may determine variations in interpretation of the responses. Bruze et al.⁴² studied the accordance in patch test readings according to the different reading systems and showed that there was good accordance among various readers, except with the NACDG system. The morphologic feature that seemed most difficult to evaluate was the papule, so, perhaps it would be convenient not to demand the existence of this feature as essential for the categorization of a patch-test reaction as allergic.

The time of patch test readings has been standardized but it has variations between different patch-test centers. Usually, the first reading is performed on day two (48 hrs) after patch test application, approximately 30 minutes after taking off the patches, and the second reading is performed at 72 or 96 hours. A delayed reading (1 week) is also recommendable because certain allergens, (e.g., neomycin, or corticosteroids, among others) may determine late positive reactions. Patch testing should be read at least in two successive opportunities, without which, their accuracy is seriously impaired. A single reading on day two (48 hrs) may determine that approximately 30% of the contact allergies detected by the standard series are missed, as compared with the number of allergies found when the test are read repeatedly up until 1 week from patch test application.⁴³ In addition, multiple readings are crucial in distinguishing false-positive irritant reactions, since the timing of these reactions is different from the allergic ones.

Problems Derived From the Assessment of Clinical Relevance of Patch Test Reactions

For clinical patch testing, validity alone is not an adequate measure of the test's utility. The confirmation of the diagnosis of contact sensitization without information regarding the relevance of the allergic reactions, fall short of its intended use. The fact that contact allergy to certain allergen(s) has been reliably demonstrated by careful patch testing does not prove that such allergen(s) is responsible

for the patient's ACD. A true positive patch test reaction only indicates that the patient has been previously exposed and sensitized to the substance. Patients may suffer major changes in their lifestyle on the basis of patch-testing results, therefore it is crucial to establish that the positive reaction is actually linked to the clinical dermatitis, either as a primary cause or as an aggravating factor. Based on the presence of a putative allergen in materials which come into contact with the skin either occupationally or during leisure activities, the pattern of distribution of the skin lesions, and the effect of elicitation by exposure and healing of the dermatitis by avoidance, positive patch-test results are judged as possible, probable or certainly relevant. According to the ICDRG criteria,^{10,44} we consider that a positive patch test reaction is "relevant" if the allergen is traced. If the source of a positive patch test is not traced, we consider it as an "unexplained positive". We refer to as "current" or "present" relevance, if the positive patch test putatively explains the patient's present dermatitis. Likewise, when the positive patch test explains a past clinical disease, not directly related to the current symptoms, we refer to this as past relevance. From a practical perspective, establishing that a positive reaction has past relevance or possible relevance does not direct the clinician to intervene directly for the very problem for which past testing was performed. Reporting data not presently relevant serves an important epidemiologic role and may be useful in preventing further outbreaks of ACD in a patient. Yet, it does not provide the information that it is essential in the management of the present problem for which the patient is being evaluated.

The determination of relevance depends primarily on the expertise of the investigator and the possibility of detecting the allergen in the environment of the patient. Many times a positive reaction is judged nonrelevant because of insufficient environmental information. We must perform a rigorous environmental evaluation, investigating the existence of allergenic exposures, characteristics of this exposure and possible concurrent factors. Relevance scores and accuracy of the assessment are significantly improved by a comprehensive knowledge of the patient's chemical environment.

If the results of the patch tests are negative for a patient for whom a diagnosis of ACD has been proposed, one has to go back to the beginning, that is, to a thoroughgoing anamnesis and physical examination. The assumed allergens should be retested (perhaps in another concentration, with another vehicle, or with another testing method) and additional allergens should be tested.^{41,45}

Besides patch testing, other types of skin tests such as open and semi-open tests, tests with product's extracts, repeated open application tests (ROAT), provocative use tests (PUT), may be required to establish a definite causative relationship between the positive patch test result and the clinical dermatitis.^{11,21,45} Use testing, such as ROAT has

significant potential in refinement of the evidence-based diagnosis of clinical relevance. This test is not standardized to the same extent and it is time-consuming, but mimics some real-life exposure situations. However, for general validation, a standardized measurement of the results of use testing like the ICDRG scoring system for patch testing is required.²¹ It has been observed to be a significant relationship between the patch test threshold and the ROAT threshold,⁴⁶ but the amount of allergen required to elicit a reaction for these two study methods is not the same. Fischer et al.⁴⁶ demonstrated that the dose per application eliciting a reaction in the ROAT is substantially lower than the dose required, eliciting a reaction in the patch test. This could be explained by the accumulation of allergen in the skin from repeated exposure and/or to the repeated stimulation of the immune system. The stronger response in the ROAT compared with the patch test threshold is relevant for risk evaluation of the elicitation potential of allergens in final products, because the same dose per unit area, eliciting a negative patch test result, might elicit a reaction when applied repeatedly in an open test.

CAN I APPLY THE TEST IN THIS SPECIFIC SITUATION? IS PATCH TESTING COST-EFFECTIVE AND SAFE IN THIS SPECIFIC PATIENT?

Whereas some studies indicate that the prognosis of ACD is poor; if the responsible allergen is identified, patient education and allergen avoidance can lead to significant improvement and even cure of the dermatitis. Accurate identification of the culprit agent and implementation of effective avoidance measures is the only significant approach in ACD treatment. Patch testing is, undeniably, the gold standard in diagnosing contact allergy, and provides a valuable mean of diagnosis that allows the physician to identify a specific chemical responsible for the dermatitis and initiate appropriate management alleviating patients' suffering without losing valuable time.⁴⁷

However, as we have discussed, the validity of diagnostic patch testing depends on the clinical circumstances, especially on a good pretest probability based on careful patients' selection. The first step in the diagnostic work out is to perform a comprehensive and standardized clinical history that covers the clinical evolution of the dermatitis and all possible etiologic factors, a complete clinical examination, and an assessment of exposure, including hazard identification, estimation of dermal exposure and risk characterization. Patch testing will be more cost-effective if we were able to fulfill a precise case definition for ACD before the test. Performing patch test as a last recourse in

patients failing to meet the case definition for ACD will hardly be cost-effective. If patch testing is performed in these patients, the practitioner should thoroughly assess the clinical relevance of all positive reactions.

The overall benefits of patch testing have been scarcely studied. Rajagopalan et al.⁴⁸ evaluated retrospectively the value of patch testing in 260 ACD patients using a standardized questionnaire and revising medical records. In this preliminary evaluation, they concluded that when patch testing is performed on patients with a prediagnosis duration of 2 months to 1 year, the postdiagnosis duration of the dermatitis was considerably decreased when comparing with the nontested patients. They suggested that patch testing should not be delayed to the extent that prognosis becomes worse in terms of chronicity of symptoms. In a subsequent multicenter observational prospective study⁴⁹, the quality-of-life outcome between patch-tested and nonpatch-tested patients was assessed using a previously validated dermatology-specific quality-of-life (DSQL) instrument. Five hundred sixty seven patients from ten centers were studied. Centers were selected to obtain a mix of stratified degrees of usage of patch testing. Data on 431 patients at the 6-month follow-up showed a significantly higher improvement in each of the DSQL domains in patch-tested patients (43% of the total group) compared with nonpatch tested subjects. In addition, a significant difference was observed in the time required to confirm the diagnosis and the proportion of subjects with confirmed diagnosis between the patch-tested and the nonpatch-tested groups.

Another important aspect to consider is patch test safety and the possibility of inducing changes in the patients' immune status. Patch testing may reactivate earlier dermatitis, boost up previous hypersensitivities, clinically silent because of a high activation threshold, elicit severe test reactions, or, what is worst, and it may actively sensitize the patients to the applied haptens. Even if active sensitization for the testing is rare, at least when testing standard allergens, we should be aware of this possibility.

Patch testing is safe and cost-effective if it is performed appropriately, patients are selected properly and a meticulous and rigorous assessment of clinical relevance of the patch test reactions is applied.

An evidence-based approach in patch testing requires an exhaustive knowledge of both clinical and diagnostic aspects of contact allergy, including the patch-test procedure and its pitfalls, as well as the potential allergens, and cross-reacting substances in domestic and occupational environments. This approach must guarantee a safe and cost-effective policy of patch testing.

What We Know

- Patch testing is currently used in clinical practice as the most important investigative and diagnostic method available for studying delayed contact hypersensitivity. It constitutes, together with a detailed clinical history and a complete physical examination, a fundamental step in the diagnostic work up of ACD.
- Several studies have shown that history and physical examination alone are not adequate to consistently and fully evaluate a patient's contact allergens. Patch testing has been shown to be significant both, in confirming contact sensitivities suspected from the clinical history and in unveiling unsuspected sensitivities.
- The outlined evidence suggests that, even if patch testing has limitations from the standpoint of its validity, it can be effectively used as a diagnostic test to establish the presence of contact sensitization to the test chemicals.
- The validity and reliability of patch testing is greater when testing allergens from the standard series, in the proper concentration and the methodology and evaluation is made according to the international guidelines such as those recommended by the ICDRG.
- If we want to maximize validity and accuracy, several aspects of the patch test procedure should be improved, including the adoption of strict criteria for the selection of patients, further standardization of the patch materials and methodology, improved use of dose response assessments, and implementation of rigorous procedures for the assessment of clinical relevance of the patch test reactions.
- Patch testing is cost-effective only if there is high pretest probability of contact sensitization. Therefore, we should always start with a careful and comprehensive clinical history, physical examination, and exposure assessment in order to produce clear-cut pretest probabilities of fulfilling the case definition for ACD, as well as better identifying the chemicals most probably relevant to the clinical dermatitis before performing the patch test.
- Patch testing results require biologic and clinical interpretation. A true positive patch test reaction only indicates that the patient has been previously exposed and sensitized to the substance and cannot be considered as a scientific proof of the patient's dermatitis unless relevance is established.
- It is indispensable to determine the relevance of the patch test reaction to the clinical situation. Patients may suffer major changes in their lifestyle on the basis of patch-testing results, therefore it is crucial to establish that the positive reaction is actually linked to the clinical dermatitis.
- When performing clinical patch testing we will always face a dilemma. Although it is true that increasing the number of tested substances will also increase the number of positive allergic reactions, it will also, because of multiple testing, give rise either to false-positives or to reactions not relevant to the specific situation. On the other hand if only small panels of chemicals are tested, selected on the basis of history of exposure, relevant allergies may be missed. This stresses the importance of always performing a meticulous assessment of the clinical relevance of the patch test reactions.
- The validity of the results will increase through the judicious use of serial dilution testing. Using a range of concentrations rather than a single concentration would be more discriminating, allowing us to better rule out false-positive reactions because of irritancy as well as establishing the elicitation threshold in allergic reactions. Ascertaining the patient's degree of sensitization may have important practical implications *vis a vis* the implementation of rational avoidance measures.
- Providing an objective proof of the allergic condition, and identifying the responsible allergen (s) patch testing is essential for a rational management of ACD patients.

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Diagnosis of Melanoma

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METHODS

One author (GW) used PubMed to search the MEDLINE database of abstracts and full-text articles using the following key words: "melanoma," "melanoma diagnosis," "melanoma epidemiology," "melanoma risk factors," and "melanoma screening." Two authors (GW, JD) reviewed the listed articles and selected only those epidemiologic and randomized control studies from 1985 to present time that were cited in at least five other publications to be used as references in this chapter.

INTRODUCTION

Melanoma arises from the malignant transformation of melanocytes. Embryologically, melanocytes are neural crest cell derivatives that migrate to the basal layer of the epidermis during development. Melanoma most commonly occurs in the skin, although it can also arise in other locations such as the eyes, ears, gastrointestinal tract, leptomeninges, and mucous membranes.

EPIDEMIOLOGY

Melanoma is the sixth most common cancer in the United States, and the incidence has more than tripled in the Caucasian population over the last 20 years.¹ Approximately 68,720 new cases of melanoma was diagnosed in the United States in 2009² The current lifetime risk for developing melanoma is 1 in 60 Americans, a 2000% increase since 1930.

While the incidence of melanoma is increasing worldwide, the highest incidence is found in Australia and New Zealand.³ According to a recent analysis of global cancer statistics from 2002, 37.7 cases per 100,000 men, and 29.4 cases per 100,000 women were reported in Australia and New Zealand, compared to 6.4 cases per 100,000 men and 11.7 cases per 100,000 women in North America.⁴

Melanoma is uncommon in children and adolescents, and approximately 90% of these cases are in those ≥ 10 years of age.⁵ An analysis of the Surveillance, Epidemiology and End Results (SEER) database showed that the incidence in those less than 20 years of age is increasing by 2.9% per year.⁶ Melanomas in children can be more advanced lesions

with a worse prognosis, perhaps a result of a delay in diagnosis or a lack of awareness.⁷

Although melanoma accounts for 4% of all skin cancers, it causes more than 74% of skin cancer deaths. In 2009, 8,650 people are expected to die from melanoma—5,550 men and 3,100 women.² Despite screening and early detection programs, the overall mortality rate from melanoma has remained stable or continues to rise.⁸ From 1969 through 1999, mortality decreased among men and women between ages of 20 to 44 years.^{8,9} However, the mortality rate among men >65 years, who make up 20% of all cases, rose by 157% during the same period.

RISK FACTORS

Numerous studies have identified risk factors for the development of melanoma. The risk factors are both genetic and environmental, likely with some interplay between the two. The major factors include excessive sun exposure, number of melanocytic nevi, cutaneous phenotype, and family and personal history of melanoma (Table 4-1).

Sun Exposure and Skin Type

Ultraviolet radiation is the main environmental factor responsible for melanoma in individuals with lightly pigmented skin. This has been supported by studies which have demonstrated an inverse relationship between latitude and melanoma incidence.¹⁰ Green or blue eyes, blond, fair, or red hair, tendency to freckle, and inability to tan are all documented risk factors.¹¹

Several case-control studies that examined the relationship between sun exposure, sunburn, and melanoma were analyzed in a systematic review.¹² Intermittent exposure and sunburn in childhood and adolescence were strongly associated with an increased risk of melanoma, while occupational exposure did not confer an increased risk.

Number and Type of Melanocytic Nevi

Epidemiologic studies have consistently shown a higher risk of melanoma with greater numbers of melanocytic nevi. In one study, the risk of melanoma was doubled in individuals

TABLE 4-1—Risk Factors for Developing Cutaneous Melanoma

Risk	Relative risk
Greatly increased risk	
Personal history of atypical moles, family history melanoma, and greater than 75–100 moles	35
Previous nonmelanoma skin cancer	17
Congenital nevus (giant, >20cm)	15-5
History of melanoma	9-10
Family history of melanoma in parent, sibling, or children	8
Immunosuppression	8-6
Moderately increased risk	
Clinically atypical nevi (2–9)	7.3-4.9
Large number of nevi (51–100)	5.0-3.0
(26–50)	4.4-1.8
Chronic tanning with UVA (PUVA treatments [>250] for psoriasis)	5.4
Modestly increased risk	
Repeated blistering sunburns	
Thrice	3.8
Twice	1.7
Freckling	3.0
Fair skin, inability to tan	2.6
Red or blond hair	2.2
Clinically atypical nevus (1)	2.3

with 50 to 99 small nevi compared with those with less.¹³ In addition, individuals with atypical nevi are at an increased risk for developing melanoma. An atypical nevus is usually larger than common nevi and also displays some degree of color variability, such as having a tan or pink shade. It also has poorly defined or “fuzzy” outer edges. In the same study cited above, the presence of a solitary atypical nevus doubled the risk of melanoma, while having >10 atypical nevi was associated with a twelve-fold elevation in risk.

Personal History of Melanoma

A personal history of melanoma is associated with an increased risk of developing a second cutaneous melanoma.^{14,15} The risk is even higher in patients who have had two primary cutaneous melanomas, as up to 30% may have a third melanoma within 5 years.¹⁶ For patients with a history of both atypical nevi and a prior cutaneous melanoma, the risk of a second primary is higher than in those with a sporadic cutaneous melanoma.¹⁷

Family History of Melanoma

Roughly 10% of melanomas are hereditary, defined as kindreds in which melanoma occurred in two or more blood relatives.¹⁸ Genetic linkage studies have identified a familial melanoma gene, CDKN2, on chromosome 9p21 which encodes the tumor suppressor protein p16.¹⁹ Mutations in this gene have been found in approximately 50% of familial melanoma patients that link to chromosome 9p.

DIAGNOSIS

Benign pigmented lesions must be distinguished from early melanoma. The ABCDs (*asymmetry, border, color, diameter*) of melanoma provide a guide for making this diagnosis.²⁰ In general, benign lesions are symmetric, have well-defined borders, are uniform in color, and are usually <6 mm in diameter. In contrast, melanomas are asymmetric, have poorly defined borders, and are more heterogeneous, with colors ranging from tan to black, often with areas

of red, white, or blue. Melanomas are often larger than 6 mm at the time of diagnosis. The ABCD checklist is diagnostic test with good sensitivity (90 to 100%, depending on whether a positive test is defined as the presence of one, two, or three of the ABCDs).²¹

Since the origin of the ABCD acronym nearly 20 years ago, evidence has accumulated that the addition of “E” for “Evolving” will significantly improve the ability of physicians and patients to recognize melanomas at earlier stages. Evolving lesions are those noted to have changed with respect to size, shape, symptoms (e.g., itching, tenderness), surface (e.g., bleeding), or shades of color.

“E” for Evolving recognizes the dynamic nature of this skin malignancy. This is especially important for the diagnosis of nodular melanomas, which frequently present at more advanced stages (i.e., thicker tumors), thus making a significant contribution to melanoma mortality rates. Nodular melanomas frequently lack asymmetry, border irregularity, color variation, and diameter greater than 6 mm. However, in one series of 125 patients, change of the lesion (i.e., evolution) was noted in 78% of nodular melanomas.²² A study by Cassileth et al. of presenting symptoms in malignant melanoma found that changes in “size, elevation and color” were the most frequent cluster of symptoms reported by patients as catalysts precipitating medical evaluation.²³

MAJOR SUBTYPES

There are four histologic subtypes of cutaneous melanoma. These include superficial spreading melanoma, nodular melanoma, lentigo maligna melanoma, and acral lentiginous melanoma. Distinction among the subtypes is based on histologic growth pattern, anatomic site, and degree of sun damage. Table 4-2 describes the epidemiologic and clinical features associated with each type.

Superficial Spreading Melanoma

Superficial spreading melanoma is the most common subtype, comprising 75% of all malignant melanomas. It is most commonly seen in individuals aged 30-50 years,

and is usually found on the trunk in men and the legs in women. Clinically, the superficial spreading type appears as a flat or slightly elevated brown plaque with variegate pigmentation. It is usually >6 mm in diameter, and may have a nodular appearance when the diameter is >2.5cm. In more advanced lesions, multiple shades of red, tan, brown, blue, black, gray, and white can be appreciated.

Nodular Melanoma

By definition, nodular melanomas are vertical growth phase melanomas.²⁴ They comprise 15 to 30% of all melanomas. They occur most often in the fifth and sixth decades of life, and are usually found on the legs and trunk. Clinically, a nodular melanoma appears as a darkly pigmented papule or dome-shaped nodule, although amelanotic variants are infrequently seen.²⁵ Rapid growth occurs over weeks to months, and this subtype is responsible for most thick melanomas.^{26,27}

Lentigo Maligna Melanoma (LMM)

LMM usually presents in the sixth or seventh decade, and is typically located on the head, neck, and arms. Most lesions begin as a freckle-like brown macule that gradually enlarges and develops darker, asymmetric foci (Figure 4-1). The radial growth phase is called lentigo maligna (LM) or Hutchinson’s freckle. The radial growth phase may last for years and never develop a vertical growth phase. Approximately 5 percent of intraepidermal lesions progress to become clinically palpable, indicating dermal invasion and transformation into lentigo maligna melanoma.²⁸ The risk of progression of LM to LMM varies with age. For a patient 45 years of age with LM, the estimated risk of developing LMM by age 75 is 3.3. For a patient 65 years of age with LM, the risk of developing LMM is 1.2%.²⁹

Acral Lentiginous Melanoma

Acral lentiginous is the least common subtype of melanoma, comprising 2-8% of all melanomas. They most commonly arise on palmar, plantar, subungual, and occasionally,

TABLE 4-2—Histologic Types of Cutaneous Melanoma

Type	Frequency(%)	Common age at diagnosis	Common Site	Clinical features
Superficial spreading	70	Mid 40s	Any	Raised border; brown lesion with pinks, whites, grays, and blues
Nodular	15	Mid to late 40s	Any	Arises from normal skin or nevus; brown to black lesion
Acral lentiginous	10	60s	Hands and feet	Flat, irregular; dark brown to black lesion
Lentigo maligna	5	70s	Face	Very irregular border; tan to brown lesion



FIGURE 4-1 Lentigo maligna melanoma. (Photo Courtesy of Ryan Ramagosa, M.D.).

mucosal surfaces. This subtype is also the most common type of malignant melanoma among Asians and dark-skinned individuals, with the sole of the foot being the most frequent site involved. Clinically, an acral lentiginous melanoma appears as a dark brown or black, unevenly pigmented patch. The sudden appearance of a pigmented band originating at the proximal nail fold (Hutchinson's sign) is suggestive of acral-lentiginous melanoma.

SCREENING

The U.S. Preventive Services Task Force reviewed the evidence in 2001, and concluded that there is insufficient evidence to recommend routine screening for skin cancer in asymptomatic patients in the primary care clinical setting.³⁰ Selective screening is ultimately the most effective in individuals with risk factors for melanoma. Compared to the general population, individuals with one or two risk factors (e.g., freckling, red or blonde hair, history of three or more blistering sunburns before 20 years of age), have 3.5 times the risk of developing melanoma, and in people with three or more risk factors, the risk is multiplied twenty-fold.³¹

In addition, detection of melanoma at an early stage saves lives; 5-year survival rates steadily decrease as the tumor thickness and stage increase. Most people with stage I lesions can expect prolonged disease-free survival and even cure, while those with thicker, advanced stage lesions (e.g., >4.0 mm) are at a higher risk to die from metastatic disease.³²

Screening examination of the entire body surface can increase the likelihood of detecting melanoma six-fold compared with partial examination. Men have more lesions on the back, and women on their lower legs, possibly because these are common areas of sunburn; screening of those sites could particularly aid early detection.³³

Skin Self Examination

A minority of individuals practice regular skin self examination (SSE), with estimates of 20%-25% in the United States.³⁴ The ability of SSE to detect melanoma and reduce morbidity and mortality has not been extensively studied. A study done by Berwick et al. reported that SSE could reduce melanoma mortality by as much as 63%.³⁵ A study in 2003 reported that regular performance of SSE was associated with a significantly reduced likelihood of having tumors >1 mm thick at diagnosis (odds ratio (OR), 0.65; 95% confidence interval (95% CI), 0.45-0.93).³⁶ The limitation of these studies is how they differ widely in their definitions of SSE and typically do not define overall practice of SSE, as specific behaviors that can be more reliably measured.

In a recent study by Swetter et al. the association between SSE practices and tumor thickness in patients with recently diagnosed melanoma was examined.³⁷ Three hundred and twenty one melanoma patients completed questionnaires on demographics and SSE practices. Patient-reported SSE was measured by routine examination of 13 specific body areas, frequency of mole examination, and use of a melanoma picture aid to assist with SSE. Patients routinely examining at least some of their skin had thinner melanomas [adjusted geometric mean tumor ratio, 0.73; 95% confidence interval (95% CI), 0.50-0.94]. Frequency of mole examination did not predict tumor thickness. Using a melanoma picture as a SSE aid was strongly associated with reduced tumor thickness (adjusted ratio, 0.75; 95% CI, 0.66-0.85 forever versus never use). A composite measure of thoroughness of SSE was the best predictor of thickness (adjusted ratio, 0.58; 95% CI, 0.36-0.75) for high versus low thoroughness.

Dermoscopy

While the ABCD rule of melanoma recognition is valuable for patient education and for all clinicians, further evaluation with dermoscopy improves the detection of melanoma. Dermoscopy refers to the use of a hand-held lens in combination with oil immersion to better view a pigmented lesion. In one report, the addition of dermoscopy for evaluation of a subgroup of clinically equivocal lesions resulted in the same high rate of specificity (99.6 versus 98.4% compared with visual examination alone), but a significant increase in positive predictive value (23 versus 6.9%).³⁸

A meta-analysis of thirteen studies³⁹ involving primarily specialist clinicians, showed that the diagnostic accuracy was significantly higher with dermoscopy than with gross visual examination (odds ratio (OR) 4.0 (95% confidence interval (95% CI), 3.0-5.1) and 2.7 (1.9-3.4), respectively). Although these studies suggested that dermoscopy had greater sensitivity for the diagnosis of MM, a randomized trial showed a 42% reduction in the number of

patients referred for biopsy in the dermoscopy arm.⁴⁰ This was consistent with the finding of a significant reduction in the benign to malignant ratio of excised melanocytic lesions from 18:1 to 4:1 (pre- and postdermoscopy eras, respectively).

Confocal Microscopy

Confocal laser scanning microscopy (CLSM) is a relatively new and advanced technique for examining pigmented lesions of the skin. CLSM obtains optical sections within intact cutaneous tissue that makes it ideally suited to the study of skin. Because melanin is refractile at near infrared wavelengths, melanocytic-derived cells are easily visualized. Preliminary studies have shown specific CLSM features of malignant melanomas and nevi that improve the diagnostic accuracy for melanocytic lesions that are difficult to diagnose.⁴¹

Langley et al. conducted a study evaluating the diagnostic accuracy of CLSM compared to dermoscopy in a prospective examination of melanocytic skin tumors.⁴² Overall, 37 melanomas and 88 nevi were studied. Morphologic CLSM criteria that were used to establish a confocal diagnosis were based on well-known criteria. Examination was performed by a single observer with

experience in CLSM. Sensitivity and specificity of dermoscopy for the diagnosis of melanoma were 89.2% and 84.1% (PPV 70.2%, NPV 94.9%), respectively. Sensitivity and specificity of CLSM were 97.3% and 83% (PPV 70.6%, NPV 98.6%), respectively. CLSM had a higher sensitivity with similar specificity compared to dermoscopy;

Early confocal microscopes were overly time consuming to use and, because of their bulky and complex configuration, could not be conveniently placed on certain anatomic areas. As a consequence, great efforts have been made to design compact instruments for use in routine clinical application. Recently, the first hand-held confocal microscope was introduced providing a small and easy to use configuration for acquisition and storage of CLSM images.

Biopsy

Suspicious lesions should undergo full-thickness biopsy. Excisional biopsy with narrow margins of 1-2 mm borders is preferred. A punch or incisional biopsy approach is appropriate when there is a low suspicion for melanoma, the lesion is large, or when it is impractical to perform an excision.⁴³ Incisional or punch biopsies should include the area of the lesion that appears most suspicious.

What We Know: Cutaneous Melanoma Diagnosis

- Incidence of cutaneous melanoma (CM) has tripled in the Caucasian population worldwide over the last two decades.
- Major risk factors for CM are:
 - Green or blue eyes; blond, red, or light hair; those with a tendency to freckle or are unable to tan.
 - Excessive ultraviolet radiation exposure in high risk individuals especially if the individual has had three or more blistering sunburns before 20 years of age
 - Greater number of melanocytic nevi or individuals with atypical nevi. Atypical nevi are usually larger than common nevi, have poorly defined or fuzzy outer edges, and display some degree of color variability including tan and pink. The presence of a solitary atypical nevi doubled the risk of CM while having 10 or more is associated with a twelve-fold increase in risk.
 - Personal history of CM. Those diagnosed with a single CM are at increased risk of developing a second and up to 30% of patients who have had two primary CM diagnoses will develop a third CM within 5 years.
 - Individuals with two or more blood relatives who have been diagnosed with CM are at increased risk.

Genetic linkage studies have identified a mutation in the gene CDKN2 in approximately 50% of familiar melanoma patients.

- The ABCDE's (Asymmetry, Border, Color, Diameter, Evolving) can be used to help identify CM. CMs are generally asymmetric, have poorly defined borders, are multicolored including tan, black, red, white, or blue, are larger than 6mm, and change size.
- Early diagnosis and prevention key to survival. Melanoma is curable if detected and surgically excised early. CM in-situ has a 99% cure rate while patients with lesions >4 mm have a 5-year survival rate of less than 50%.

Detection in those with a stage 1 lesion can expect prolonged disease-free survival or be cured while those diagnosed with thicker, more advanced stage lesions are at higher risk of mortality.

- Suspicious lesions should undergo full-thickness biopsy and an excisional biopsy with narrow margins (1-2 mm borders) is preferred. A punch or incisional biopsy can be used when there is low suspicion of melanoma, the lesion is large, or it is impractical, but should include the area that appears most suspicious.

The prognosis of melanoma is related to tumor thickness. Depth for depth, all melanomas have the same metastatic potential, regardless of subtype. Melanoma is curable if detected early and surgically excised. Melanoma in-situ has a 99% curability rate, and patients with thin lesions (< 0.75 mm) have a 5-year survival rate of > 98%. This is in contrast to patients with thicker lesions (> 4 mm) who have 5-year survival rate of less than 50%.

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Diagnosis of Cutaneous T-Cell Lymphoma

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INTRODUCTION

Cutaneous T cell lymphomas (CTCLs) are extranodal non-Hodgkin's lymphomas arising primarily in the skin.¹ Mycosis fungoides (MF) and the more aggressive Sézary Syndrome (SS) constitute the majority of clinically encountered forms of CTCL.² Thus, the emphasis of this chapter will be on these two forms of CTCL, although other forms of CTCL will also be briefly touched upon.

The initial diagnosis of early MF is sometimes difficult, especially in early stages, as plaque and patch lesions often resemble benign dermatoses.³ Hence, from 1999 through 2004, the International Society for Cutaneous Lymphoma (ISCL) conducted a series of five meetings to review criteria and develop a method for diagnosing early MF. A report was issued in 2005, summarizing the conclusions of the meetings, and in this chapter, we utilize the findings as a foundation upon which we delve into a discussion of the evidence-based diagnosis of CTCL.³ Compared to other diseases, and certainly for those utilizing clearly defined lab values as criteria for the inclusion/exclusion of disease, the diagnosis of CTCL is more subjective, but an understanding of the evidence behind each set of criteria will hopefully benefit both the clinicians and patients.

The ISCL algorithm for the diagnosis of early mycosis fungoides includes clinical, histopathologic, molecular,

and immunopathologic criteria. A scoring system was proposed in which a score of or greater out of a total possible score of 6 was "consistent with" a diagnosis of mycosis fungoides. Each of these criteria will be reviewed separately in the sections that follow.

With respect to clinical criteria, patients received a score of 2 if they had persistent and/or progressive patches or thin plaques as well as at least 2 of the following additional criteria: lesions located in a nonphotoexposed area, variation in lesion size or shape, or poikiloderma. If patients had only 1 of these additional criteria, in addition to persistent or progressive plaques, they only received a score of 1. Histologically, if patients had superficial lymphoid infiltrates along with epidermotropism in the absence of spongiosis, as well as atypical lymphocytes, they received a histological score of 2. If patients had only atypical lymphocytes or epidermotropism in the absence of spongiosis, they received a histologic score of 1. With respect to molecular studies, if patients had a T cell receptor (TCR) gene rearrangement, they received 1 point. Flow cytometry/phenotypic analyses resulted in patients receiving 1 point if they had any of the following: > 50% loss of CD2, CD3, and/or CD5 on T cells, < 90% loss of CD7 on T cells, or discordance of epidermal and/or dermal expression of CD2, CD3, CD5, or CD7. These criteria are summarized in Table 5-1.

TABLE 5-1—Proposed Criteria for Diagnosis of Early Mycosis Fungoides

Maximum # Points	Required Finding	Additional Findings	# Points
Clinical: 2	Persistent and/or progressive patches or thin plaques	Lesions located in a non-photo-exposed area	1
	Persistent and/or progressive patches or thin plaques	Variation in lesion size or shape	1
	Persistent and/or progressive patches or thin plaques	Poikiloderma	1
Histologic: 2	Superficial lymphoid infiltrate with epidermotropism	Absence of spongiosis	1
	Superficial lymphoid infiltrate with epidermotropism	Atypical lymphocytes	1
Molecular: 1	Positive T cell receptor gene rearrangement	N/A	1
Phenotypic: 1	> 50% loss of CD2, CD3, and/or CD5 on T cells	N/A	1
	< 90% loss of CD7 on T cells	N/A	1
	Discordance of epidermal and/or dermal expression of CD2, CD3, CD5, or CD7	N/A	1
Total 6			

(Adapted from a 2005 report of the International Society of Cutaneous Lymphomas.³)

TABLE 5-2—Proposed Definitions of Erythrodermic Cutaneous T Cell Lymphomas			
	Existence of mycosis prior to presentation	Presence of leukemic cells in blood	B Stage (T4 N0-3 M0-1)
Sézary syndrome	Rarely	Yes	2
Erythrodermic mycosis fungoides	Yes	None or very little	0-1
Erythrodermic mycosis fungoides, not otherwise specified	No	None or very little	0-1

(Adapted from a 2002 report of the International Society of Cutaneous Lymphomas.⁴)

For the diagnosis of advanced MF and SS, the ISCL issued a report in 2002 after meeting twice to discuss criteria for diagnosing erythrodermic cutaneous T cell lymphomas (E-CTCL).⁴ The proposed definitions of the various forms of E-CTCL are depicted in Table 5-2.⁴ Blood involvement grading (B1 vs. B2) is depicted in Table 5-3, with B0 signifying no blood involvement. In the following sections of this chapter, we will review some of the evidence supporting the recommendations outlined by the ISCL.

TABLE 5-3—Summary of Proposed Criteria for Evaluating B1 vs. B2 Designation in Staging of Erythrodermic CTCL. (Adapted from a 2002 Report of the International Society of Cutaneous Lymphomas⁴)

	Blood Involvement	Criteria
B1	Minimal	<ul style="list-style-type: none"> • At least 5% Sézary cells (blood smear) and positive T cell receptor gene rearrangement or other evidence of a clonal population • At least 20% Sézary cells (blood smear)
B2	Leukemic	<ul style="list-style-type: none"> • Absolute count of at least 1000/mm³ • CD4:CD8 ratio of at least 10:1 due to an increase in CD3+ or CD4+ cells via phenotypic analysis (flow cytometry) • Positive T cell receptor gene rearrangement (PCR or Southern blot) • Abnormal T cell clone by cytogenetic analysis (FISH) • Phenotypic aberrations (CD2, CD3, CD4, CD5), CD7 loss on T cells, or greater than 40% CD4⁺CD7⁻ cells

CTCL, cutaneous T cell lymphomas.

CLINICAL CRITERIA

Although research has shown that the majority of patients with CTCL do not die from their disease, the survival of patients with MF and SS has been shown to decrease with increasing skin stage.⁵ Earlier diagnosis could, therefore potentially increase survival because the risk of progressing to extracutaneous disease in MF patients increases with skin stage, although roughly 9% of early stage MF patients progress to higher stages even with treatment.^{6,7} Because recognition of early stage CTCL can be difficult, given that it may mimic other dermatoses clinically and histologically, a higher index of suspicion may be needed to initiate a more extensive work-up.^{8–10} Many of the recommendations made by the National Comprehensive Cancer Network (NCCN) regarding the essential diagnostic work-up of MF and SS are based on lower-level evidence and clinical experience.¹¹ However, there are research-based, key elements in taking a history, performing a physical examination, and ordering laboratory studies, which may facilitate the physician in making a more timely diagnosis of CTCL.

History

The index of suspicion for CTCL will vary depending on the experience of the clinician, the history of present illness and the clinical presentation. For patients suspected of having CTCL, an accurate list of medications including commencement dates should be elicited, as certain medications can produce a pseudolymphoma (Table 5-4), as well as other drug-induced reactions which may mimic CTCL.¹² Discussion of whether a trial off the medication(s) has been attempted and the response should be recorded.³ A history of prior tick bites may also be pertinent, especially in a patient with unilesional lesions, as tick bites may stimulate lymphoproliferative disorders such as a CD30+ lymphoproliferative disorder.¹³

When eliciting a history in a patient suspected of having MF, it is important to note the persistent nature of the lesions or an increase in the size or number of lesions.³ The presence of B-symptoms should also be recorded. Fever, fatigue, and weight loss may accompany certain CTCL subtypes,

TABLE 5-4—Medications which may Simulate MF or Cause or Predispose Patient to Pseudolymphoma

Carbamazepine ^{12,37}
Phenytoin ^{37,38}
Clonazepam ³⁹
Fluoxetine ³⁹
Antihistamines ⁴⁰
Atenolol ⁴¹

MF, mycosis fungoides.

such as subcutaneous panniculitis-like T-cell lymphoma,¹⁵ or may suggest a systemic lymphoma with secondary cutaneous involvement. Patients with SS will also typically complain of an intense pruritus. In general, however, pruritus is nonspecific and may or may not accompany CTCL.

Physical Examination

The presentation of the patient to the physician's office will obviously dictate the work-up. The evaluation of an erythrodermic patient suspected of having Sézary syndrome will differ from the referred patient with an "atypical lymphoid infiltrate" suspicious for CTCL. This is the reasoning for presenting the typical clinical features of the CTCL

subtypes separately (Table 5-5). However, in general a complete skin examination is recommended for anyone suspected of having CTCL. Common sense mandates an examination of lymph node regions, because detection of lymphadenopathy may provide clues to an alternative diagnosis or may be used in staging purposes if a diagnosis of CTCL is confirmed. An abdominal examination should also be performed to evaluate for organomegaly, as visceral involvement may occur in later stages of disease or may be concurrent in other lymphomas with cutaneous involvement (secondary cutaneous lymphomas). Examination of the oral and nasal cavities may also be appropriate depending on the patient's presentation as CTCL sub-types may affect these areas.

TABLE 5-5—Physical Examination Findings

CTCL subtype	Typical morphology of lesions, associated skin findings	Common Distribution	Extracutaneous spread
Mycosis fungoides	Patches, infiltrated plaques, and tumors; poikiloderma and variation in size and shape are common. ³	Tendency to appear initially on non-sun exposed areas ³	Lymph node and visceral involvement may be present in later stages ¹⁴ ; can involve the oral cavity ⁴²
Folliculotropic MF	Typically patches, plaques, follicular papules, nodules/tumors, acneiform lesions ^{14,43} ; alopecic eyebrows with plaques noted to be common ⁴³	Thicker plaques and tumors may favor the head and neck region; thinner plaques and patches may be occur on the trunk and extremities ⁴³	Concurrent lymph node involvement and visceral involvement reported ⁴³
Pagetoid reticulosis	Typically presents with one 'psoriasiform' patch or plaque ¹⁴	Classically on the extremities ¹⁴	Not reported ¹⁴
Granulomatous slack skin	Patches, plaques, and skin laxity/bulky skin folds in intertriginous areas ^{14,44}	Skin laxity typically in intertriginous areas ⁴⁴ , with preferential involvement of the axillary regions ¹⁴	No evidence of definitive extracutaneous spread found in a review of the literature; reference reviewed herein reported 4 cases with no extracutaneous disease ⁴⁴
Primary cutaneous anaplastic large cell lymphoma	Single or multiple nodules, tumors, and sometimes papules, which may show ulceration; may spontaneously regress ¹⁴	No preferential anatomic site ⁴⁵	Extracutaneous spread in roughly 10% of patients, mostly with lymph node involvement ¹⁴
Lymphomatoid papulosis	Papular, papulonecrotic, and nodular skin lesions in multiple growth phases characteristic; lesions may show spontaneous regression but typically recur and are chronic ¹⁴	Mainly on trunk and limbs ¹⁴ , but may not preferentially involve any site ⁴⁶	LyP is not classically thought to spread extracutaneously; although in a small minority of patients a systemic lymphoma may be associated with a history of LyP ^{14,46}
Subcutaneous panniculitis-like T-cell lymphoma	One to several nodules and plaques ¹⁴	Preferential involvement of the lower extremities, although disseminated disease can occur ¹⁴	Extracutaneous spread rare ¹⁴
Primary cutaneous CD4+ small/medium pleomorphic T-cell lymphoma	Solitary plaque or tumor ¹⁴	Superior trunk, face, or neck ¹⁴	Lymph node involvement rare if ever as studies have shown no lymph node or bone marrow involvement ⁴⁷
Sézary syndrome	Erythroderma; frequently marked exfoliation, eyelid ectropion, marked pruritus, alopecia, edema, keratoderma, and fissuring on palms and soles; dystrophic nails common. ^{14,34}	Generalized (for erythroderma); fissuring on palms and soles ¹⁴	Lymph node involvement ¹⁴ ; bone marrow involvement rare ³⁶ ; blood involvement by definition

(Continued)

TABLE 5-5—Physical Examination Findings (Continued)

CTCL subtype	Morphology of lesions, associated skin findings	Common Distribution	Extracutaneous spread
Extranodal NK/T-cell lymphoma, nasal-type	Multiple plaques or tumors ¹⁴	Trunk and extremities; facial distribution in nasal-type ¹⁴	Cases with skin involvement may also involve the liver, spleen, bone marrow, and testes ⁴⁸
Primary cutaneous aggressive CD8+ T-cell lymphoma	Papules, nodules, and tumors with ulceration or necrosis, or with patches and plaques ¹⁴	No preferential site found in a review of the literature	Lymph nodes may be unininvolved; spread to testis, lung, and CNS reported ⁴⁹
Primary cutaneous γ/δ T-cell lymphoma	Ulcerated plaques and tumors ¹⁴	Preferential involvement of the extremities; may be disseminated ¹⁴	Lung, liver, and spleen involvement have been reported ⁵⁰ , but lymph node involvement rare ¹⁴
Primary cutaneous peripheral T-cell lymphoma, unspecified	Nodules or tumors are typically present in patients who carry this diagnosis; lesions may be solitary, localized, or generalized ¹⁴	No preferential site ¹⁴	Systemic disease may develop in patients diagnosed as having an unspecified primary cutaneous T-cell lymphoma ⁵¹
Adult T-cell leukemia/lymphoma smoldering variant or cutaneous-type	Nodules or tumors, generalized papules, or plaques ¹⁴ ; may rarely present as solitary nodule ⁵²	No preferential site found in a review of the literature.	Cases classified as a cutaneous-type of ATLL have been described with only cutaneous involvement (i.e. lack of lymph node or blood involvement) ⁵² ; however, skin lesions in ATLL are generally associated with disseminated disease ¹⁴

MF, mycosis fungoides; LyP, lymphomatoid papulosis; ATLL, adult T-cell leukemia/lymphoma

Laboratory and Ancillary Testing

A complete blood count (CBC) with differential and comprehensive metabolic panel (CMP) is indicated in the evaluation of patients with suspected CTCL. These tests may be beneficial in detecting other diseases (e.g., hepatitis or renal disease), or in distinguishing CTCL subtypes. For example, ATLL, which may resemble MF, may present with hypercalcemia and leukocytosis.¹⁴ In order to diagnose SS based on the proposed criteria formulated by the International Society for Cutaneous Lymphomas (ISCL), erythroderma accompanied by at least one of the following must be present: (1) an absolute Sézary count of ≥ 1000 cells/mm³; (2) a CD4/CD8 ratio ≥ 10 because of an increase in CD3+ or CD4+ cells by flow cytometry; (3) abnormal expression of T-cell markers by flow cytometry; (4) elevated lymphocyte count with a hematologic-based T-cell clone; (5) or a “chromosomally abnormal T-cell clone”.⁴ Based on the proposed ISCL criteria alone, erythrodermic patients suspected of having SS will require a CBC with differential, flow cytometry, a possible blood smear, and/or a Southern blot or PCR to detect a T-cell clone. The NCCN guidelines support the acquisition of the aforementioned studies in nondiagnostic skin-biopsies of patients with suspected MF and SS, especially in those patients who present with erythema covering greater than 80% of the body surface area.¹¹

A lymph node biopsy may also be performed when a definitive diagnosis is lacking.¹¹ Before a biopsy of a suspected skin lesion is performed, it may be important to

discontinue topical steroids for a short period of time prior to the biopsy (i.e. anecdotally for approximately two weeks prior to the biopsy). Skin scrapings may also be performed in select cases as tinea corporis may mimic MF.³

HISTOLOGIC

The initial evaluation of MF represents a diagnostic challenge for dermatopathologists. The classic histopathologic appearance of MF in its advanced plaque stages demonstrates: (1) lymphocytes with marked cellular atypia and cerebriform nuclei (“Sézary cells”), and (2) a band-like lymphocytic infiltrate in the upper dermis, the dermal-epidermal junction, and epidermis (“epidermotropism”).¹⁵ While histologic evaluation of advanced MF is relatively straightforward, in its early stages, the histologic features of MF are notoriously difficult to differentiate from benign inflammatory dermatoses and lymphoid hyperplasias.^{3,16} Moreover, MF evolves slowly, and patients often carry a long-standing diagnosis of eczema or parapsoriasis.¹⁶ For these reasons, the reproducibility and concordance rates among pathologists in the diagnosis of early MF are low.^{17,18}

In an effort to standardize reporting of MF lesions, The International Society for Cutaneous Lymphoma has advocated an integrated grading system developed by Guitart et al. in 2001 for the histologic evaluation of biopsies suspicious for MF.³ This grading system, summarized in Table 5-6, is based on the sequential evaluation of major and minor histologic criteria reflecting the pathologist’s degree

TABLE 5-6—Criteria for the Diagnosis of Mycosis Fungoides¹⁶

I. Major Criteria	
Low Power	Density
0 = Scant infiltrate	
1 = Mild perivascular superficial infiltrate	
2 = Moderately dense perivascular or band-like infiltrate without thickening of papillary dermis	
3 = Dense, confluent infiltrate with thickening of the papillary dermis and involvement of the reticular dermis	
Medium Power	Epidermotropism
0= None	
1 = Focal basal epidermotropism and/or single Pautier microabscess or a few couplets/triplets or scattered lymphocytes without spongiosis	
2 = Extensive basal epidermotropism and/or two or more Pautier microabscesses	
3 = Extensive epidermotropism with more lymphocytes than keratinocytes	
High Power	Atypia
0 = No atypia	
1 = Mild atypia (small and intermediate cells)	
2 = Moderate atypia (small, intermediate, <i>plus</i> large atypical cells)	
3 = Uniformly atypical or pleomorphic cells, many mitotic figures, few small round reactive lymphocytes. Lymphocytes are mostly intermediate or large in size.	
Minor Criteria	
1=Reticular fibroplasia of the papillary dermis around single lymphocytes (wiry collagen)	
1 = Primarily low-grade intraepidermal atypical lymphocytes	
2 = Primarily high-grade intraepidermal atypical lymphocytes	
1 = Lymphocytic infiltrate <i>without</i> inflammatory features:	
— edema of the papillary dermis	
— mixed inflammatory infiltrate (eosinophils, PMNs)	
— spongiosis	
— margination of neutrophils without prominent endothelial cells	

of diagnostic certainty. Diagnosis is obtained by adding the component scores. Based on the total score, lesions are evaluated as: (1) perivascular/interface lymphocytic dermatitis (total score = 0-2 points); (2) atypical lymphocytic infiltrate (MF cannot be excluded) (total score = 3-4 points); (3) atypical lymphocytic infiltrate suggestive of MF (total score = 5-6 points); or (4) MF (total score = 7-13 points).¹⁶

Guitart et al. showed improvement in the agreement rate among pathologists trained to use this grading system (precision rated kappa = 0.854), as compared to independent assessment alone (precision weighted kappa = 0.630).¹⁶ However, as is true of all of the histopathologic studies to date, the Guitart grading system has not yet seen widespread use or been validated by others.³

Only three studies since 2000 have examined the efficacy of histologic criteria visible on hematoxylin and eosin staining in diagnosing early MF.¹⁸⁻²⁰ These retrospective case series used univariate analyses to determine significant criteria distinguishing early-MF from non-MF lesions. The sensitivity, specificity, and results of univariate analysis in these studies are summarized in Table 5-7. Histologic features that were specific for early MF in at least two of the three studies included Pautrier's microabscesses and haloed lymphocytes. Features that were sensitive for early MF in at least two of the three studies included monomorphic lymphocytic infiltrates and disproportionate epidermotropism. Two studies examined whether histologic criteria that were shown to be significant on univariate

analysis had additional discriminating power on multivariate analysis. Naraghi et al. found that no criteria had additional discriminating power, while Santucci et al. found that five criteria were independently associated with early MF cases ($p < 0.001$): epidermal medium-large cerebriform cells, dermal medium-large cerebriform cells in clusters, absence of papillary dermis fibrosis, epidermotropism with lined single cells, and absence of dermal blast-like cells.^{18,19}

The efficacy of immunohistochemical staining in diagnosing early MF is an emerging area of interest. In a retrospective study of T cell markers on paraffin-embedded sections of MF lesions and benign inflammatory dermatoses, Cotta et al. showed that CD7 immunolabeling was

significantly lower in the MF group compared to the benign dermatoses group ($p = 0.04$). In the MF lesions, the difference between the number of CD3- and CD7-positive cells was significant (86.45% for CD3 and 53.87% for CD7; $p < 0.001$), while in the benign inflammatory lesions, there was no significant difference (79.09% for CD3 and 73.63% for CD7; $p = 0.669$).²¹

Finally, subsequent to the International Society for Cutaneous Lymphoma report, a study by Ismail et al. reviewed a group of 92 patients with suspected MF to definitive MF, graded on a scale from 1 (not MF) to 7 (definitive MF), on the basis of clinical and histologic data.²² They then correlated surface CD7 expression or loss by flow

TABLE 5-7—Results of Three Retrospective Studies of the Efficacy of Histologic Criteria for Differentiating Early MF from Non-MF Lesions

Author(s)	Histologic Criterion	Sensitivity (%)	Specificity (%)	P-value
Santucci et al. ⁵³	Epidermotropism: Single cells	58.3	30.8	NR
	Epidermotropism: Linearly arranged single cells	45.8	100	0.00316
	Epidermotropism: Pagetoid spread	33.3	100	0.03242
	Epidermotropism: Tiny collections	41.7	46.2	NR
	Epidermotropism: Pautrier microabscesses	4.2	100	NR
	Epidermal cerebriform cells: common type	100	7.7	NR
	Epidermal cerebriform cells: Medium-large	100	92.3	0.00001
	Dermal medium-large cerebriform cells: Single	100	15.4	NR
	Dermal medium-large cerebriform cells: Cluster	91.7	100	0.00001
	Absence of dermal blast-like cells	41.7	100	0.00670
	Absence of spongiotic microvesicles	95.8	23.1	NR
	Monomorphic dermal infiltrate (vs mixed)	91.7	61.5	0.00107
	Band-like infiltrate (vs perivascular)	58.3	15.4	NR
	Pattern: Superficial perivascular	25.0	92.3	NR
	Pattern: Spongiotic psoriasiform	16.7	92.3	NR
	Pattern: Psoriasiform lichenoid	8.3	76.9	NR
	Pattern: Spongiotic lichenoid	41.7	53.8	NR
	Pattern: Atrophic lichenoid	8.3	84.6	NR
	Absence of papillary dermis edema	66.7	53.9	NR
	Absence of papillary dermis fibrosis	66.7	100	0.00012
Naraghi et al. ¹⁹	Atrophy	42	50	NR
	Acanthosis	67	50	0.77
	Parakeratosis	54	67	0.38
	Spongiosis	54	25	0.22
	Pautrier's microabscesses	37.5	100	0.002
	Disproportionate epidermotropism	75	92	0
	Haloed lymphocytes	87.5	67	0
	Epidermal > dermal lymphocytes	41	100	0.001
	Hyperconvoluted epidermal lymphocytes	62.5	75	0.019
	Intensity dermal infiltrate	87.5	25	0.46
	Hyperconvoluted dermal lymphocytes	83	87.5	0
	Telangiectasia	100	8	0.489
	Papillary dermal fibrosis	96	50	0
	Pattern of epidermotropism: single basal	79	12.5	0.35
	Pattern of epidermotropism: pagetoid	8	100	NR
	Pattern of epidermotropism: mixed	12.5	87.5	NR
	Dermal infiltrate: monomorphic	71	37.5	0.76
	Dermal infiltrate: polymorphous	29	62.5	NR
	Dermal lymphocytes: small	83	0	NR
	Dermal lymphocytes: small, medium	12.5	100	0.113
	Dermal lymphocytes: medium	4	100	NR

(Continued)

TABLE 5-7—Results of Three Retrospective Studies of the Efficacy of Histologic Criteria for Differentiating Early MF from Non-MF Lesions

Author(s)	Histologic Criterion	Sensitivity (%)	Specificity (%)	P-value
Inchara and Ralajakshmi ²⁰	Epidermotropism	100	87	0
	Lymphocyte tagging	96	87	0
	Pautrier microabscesses	41	96	0
	Haloed lymphocytes	58	96	0
	Disproportionate epidermotropism	82	93	0
	Larger epidermal lymphocytes	70	96	0
	Convolute lymphocytes	47	100	0
	Monomorphic infiltrate	88	45	0.017
	Involvement of papillary and reticular dermis	47	84	0.015
	Wiry collagen	54	90	0.001
	Absence of dermal edema	100	100	0.004
	Eccrine infiltration	17	100	0
	Mucin within follicle	17	100	0
	Follicular infiltration	35	96	0.002
	Pattern: Spongiotic lichenoid	NR	NR	0.218
	Pattern: Spongiotic psoriasiform	NR	NR	0.373
	Pattern: Lichenoid psoriasiform	NR	NR	0.163
	Absence of spongiosis	NR	NR	0.100
	Pagetoid spread	NR	NR	0.196
	Interface dermatitis	NR	NR	0.600
	Elongated parakeratosis	NR	NR	0.500

MF, mycosis fungoides; NR, not reported.

cytometry, the presence, or absence of a TCR gene rearrangement, and CD45RB⁺/CD45RO⁻ staining pattern in formalin-fixed paraffin embedded biopsy samples with the numerical score for each of the 92 patients.²² They found that in cases of definitive MF, > 90% CD7 loss (100.0% of patients) correlated well with high CD45RB expression but marked CD45RO loss in the epidermotropic atypical lymphocytic cells in biopsied lesions (85.5% of patients) and less so with a positive TCR gene rearrangement

(57.1% of patients).²² In cases of probable MF, such as in patients with a score of 4, > 90% CD7 loss (83.3% of patients) again correlated well with CD45RB positivity but CD45RO loss in epidermotropic cells (83.3% of patients) and less so with positive TCR gene rearrangement studies (58.3% of patients).²² These results (Figure 5-1) suggest that CD45RB and CD45RO immunostaining in formalin fixed paraffin embedded sections could be proposed as a future criterion to aid in the diagnosis of MF.

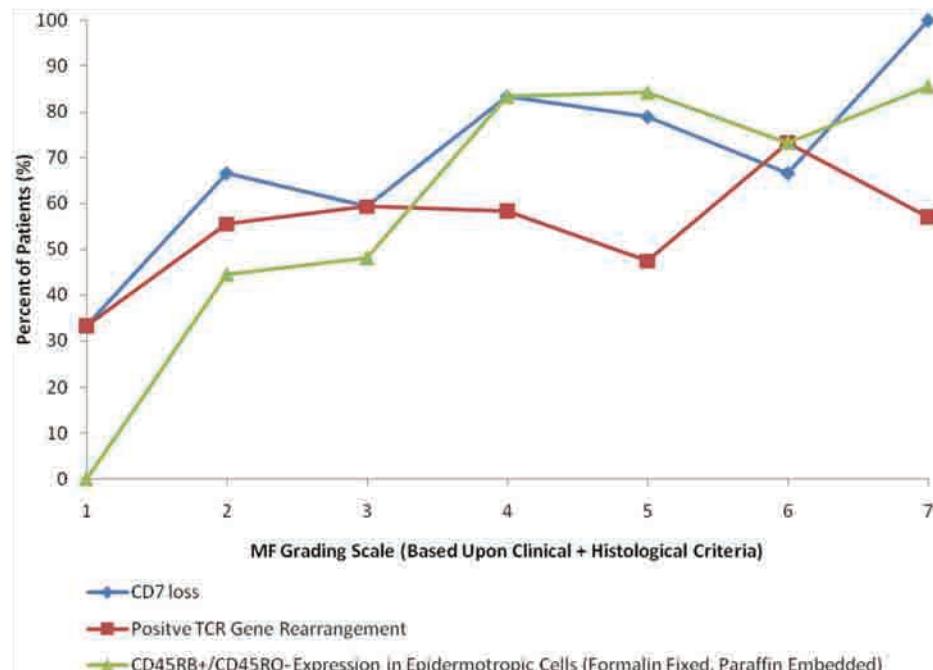


FIGURE 5-1 Summary of data comparing MF grade with the percentage of patients with > 90% CD7 loss by flow cytometric analysis of cells from frozen biopsies of lesions, positive TCR gene rearrangements, and a specific pattern of marked CD45RO loss but CD45RB positivity in epidermotropic cells.²²

MOLECULAR

As noted in the introduction, in the early stages of cutaneous T-cell lymphoma, clinical diagnosis is difficult. The lesions in early CTCL can be difficult to distinguish from benign inflammatory dermatoses, and histopathologic distinction between CTCL and benign lymphocytic infiltrates can be challenging. Hence, the use of validated diagnostic tools to aid in distinction of these diseases. While immunophenotypic findings (discussed in following

section) can help distinguish benign from malignant processes, they are frequently insufficient for definitive diagnosis. Demonstration of clonality via T cell receptor gene rearrangements further supports a diagnosis of malignancy.

There are several polymerase chain reactions (PCR)-based clonality assays available for detection of T-cell clonality. Each method has unique advantages and drawbacks.²³ A Medline search of “TCR gene rearrangement CTCL” revealed 52 results. Table 5-8 summarizes the applicable studies.

TABLE 5-8—Summary of T Cell Receptor Gene Rearrangement Studies

Author(s)	Diagnosis (# of patients)	Assay(s) used	Findings	Comments																				
Algara et al. ⁵⁴	Early MF (8), SS (2), Non-MF TCL (2) LyP (3) Benign (11)	PCR on frozen tissue samples	<u>Monoclonal TCR GR detected in:</u> 7/8 (88%) early MF 1/2 (50%) SS 2/2 (100%) non-MF TCL 2/3 (67%) lymphomatoid papulosis 0/11 (0%) benign																					
Andersen et al. ⁵⁵	CTCL (12), Suspicious for CTCL (1), Granulomatous slack skin (1), Inflammatory skin disease (8)	PCR-DGGE on archived paraffin-embedded tissue	9/12 (75%) CTCL 1/1 (100%) granulomatous slack skin																					
Ashton-Key et al. ⁵⁶	MF (27), Pre-MF (22), Borderline (32), Chronic dermatitis (31)	PCR on archived formalin-fixed paraffin-embedded tissue	<u>Monoclonality in:</u> 59% MF 50% pre-MF 19% borderline																					
Bakels et al. ⁵⁷	PseudoT-cell lymphoma (11), CTCL (17)	PCR/DGGE analysis using primers recognizing TCR V γ_{1-8} genes	<u>Clonality:</u> 15/17 CTCL (88%), including 4/6 (67%) patch/plaque-stage MF & 11/11 (100%) tumor-stage MF & pleomorphic CTCL vs. 0/10 (0%) pseudo-TCL																					
Fucich et al. ⁵⁸	CTCL (45), Indeterminate (24), Benign (11)	PCR	Presence of clonal T cell expansion: <table border="1"> <thead> <tr> <th></th> <th>-</th> <th>β</th> <th>γ</th> <th>$\beta \& \gamma$</th> </tr> </thead> <tbody> <tr> <td>CTCL</td> <td>9 (20%)</td> <td>6 (13%)</td> <td>12 (27%)</td> <td>18 (40%)</td> </tr> <tr> <td>Indeter- minate</td> <td>6 (25%)</td> <td>1 (4%)</td> <td>10 (42%)</td> <td>7 (29%)</td> </tr> <tr> <td>Benign</td> <td>9 (82%)</td> <td>0 (0%)</td> <td>0 (0%)</td> <td>2 (18%)</td> </tr> </tbody> </table>		-	β	γ	$\beta \& \gamma$	CTCL	9 (20%)	6 (13%)	12 (27%)	18 (40%)	Indeter- minate	6 (25%)	1 (4%)	10 (42%)	7 (29%)	Benign	9 (82%)	0 (0%)	0 (0%)	2 (18%)	
	-	β	γ	$\beta \& \gamma$																				
CTCL	9 (20%)	6 (13%)	12 (27%)	18 (40%)																				
Indeter- minate	6 (25%)	1 (4%)	10 (42%)	7 (29%)																				
Benign	9 (82%)	0 (0%)	0 (0%)	2 (18%)																				
Dommann et al. ⁵⁹	MF (6), Non-MF CTCL (4), SS (7), PSL (8), LyP (1)	Southern blot	<u>Clonal TCR-β GR found in skin:</u> 4/5 (80%) MF 7/7 (100%) SS 2/4 (50%) non-MF CTCL 0/8 (0%) PSL & 0/1 (0%) LyP																					
Graf et al. ⁶⁰	CTCL (24)		92% demonstrated clonality																					
Khalil et al. ⁶¹	CTCL (66), Benign (58)	PCR for TCR- γ then gel electrophoresis	87.1% sensitivity & 92% specificity for detecting clonal T-cell GR among CTCL cases, with PPV-93.1% & NPV-85.2%																					
Klemke et al. ⁶²	Parapsoriasis (26), Early-stage MF (12)	PCR-GSA	<u>Monoclonality detected in skin of:</u> 5/26 (19.2%) parapsoriasis 8/12 (66.7%) early MF																					
Murphy et al. ⁶³	Suspected patch stage MF (22), Inflammatory dermatoses (15)	Nonradioactive PCR-SSCP	<u>Monoclonality detected in skin of:</u> 17/22 (77%) MF 0/15 (0%) controls																					
Nakajima et al. ⁶⁴	MF (10), Parapsoriasis en plaque (1), Adult T-cell leukemia/lymphoma (10), CTCL (1), LyP (4), B-cell lymphoma (4), Actinic reticuloid (2)	Southern blot	<u>Monoclonality in:</u> 4/10 (40%) MF skin biopsies (all patients with a detectable clonal population were Stage IIIB or greater; all patients without a detectable clonal population were Stage IIA or less), 9/10 (90%) ATL skin biopsies; 1/1 (100%) Other CTCL; 1/4 (25%) LyP; 4/4 (100%) CBCL; 0/2 (0%) actinic reticuloid																					

(Continued)

TABLE 5-8—Summary of T Cell Receptor Gene Rearrangement Studies (Continued)

Author(s)	Diagnosis (# of pts)	Assay(s) used	Findings	Comments																		
Plaza et al. ⁶⁵	CTCL (23), Other (57)	PCR	Monoclonal TCR- β GR found in: 21/23 (91.3%) CTCL 12/33 (36.3%) primary cutaneous lymphoid dyscrasias 5/16 (31.3%) drug-associated 1/8 (12.5%) reactive lymphoid hyperplasia																			
Ponti et al. ⁶⁶	CTCL (194), Benign (353)	Multiplex PCR/HD analysis	Dominant T-cell clone found in: 162/194 (83.5%) CTCL 8/353 (2.3%) benign inflammatory disease	92.7% diagnostic accuracy (p<0.001)																		
Sandberg et al. ⁶⁷	CTCL (31), Benign dermatoses (12)	Southern blot vs. various PCR methods	Clonal TCR GR in skin: <table border="1"> <thead> <tr> <th></th> <th>All CTCL</th> <th>Benign</th> </tr> </thead> <tbody> <tr> <td>PCR/HD</td> <td>TCR-γ: 17/26 (65%)</td> <td>1/12 (8%)</td> </tr> <tr> <td></td> <td>TCR-β: 15/26 (58%)</td> <td></td> </tr> <tr> <td>PCR/GS</td> <td>TCR-γ: 19/26 (73%)</td> <td>1/12 (8%)</td> </tr> <tr> <td></td> <td>TCR-β: 16/26 (62%)</td> <td></td> </tr> <tr> <td>SB</td> <td>TCR-β: 20/29 (69%)</td> <td>0/12 (0%)</td> </tr> </tbody> </table>		All CTCL	Benign	PCR/HD	TCR- γ : 17/26 (65%)	1/12 (8%)		TCR- β : 15/26 (58%)		PCR/GS	TCR- γ : 19/26 (73%)	1/12 (8%)		TCR- β : 16/26 (62%)		SB	TCR- β : 20/29 (69%)	0/12 (0%)	
	All CTCL	Benign																				
PCR/HD	TCR- γ : 17/26 (65%)	1/12 (8%)																				
	TCR- β : 15/26 (58%)																					
PCR/GS	TCR- γ : 19/26 (73%)	1/12 (8%)																				
	TCR- β : 16/26 (62%)																					
SB	TCR- β : 20/29 (69%)	0/12 (0%)																				
Scheller et al. ⁶⁸	CTCL (53), Benign dermatoses (27)	PCR on formalin-fixed, paraffin-embedded skin bx	Clonal TCR- γ GR found in: <table border="1"> <thead> <tr> <th></th> <th>CTCL</th> <th>Benign</th> </tr> </thead> <tbody> <tr> <td>HD-MDE PAGE</td> <td>22/53 (41.5%)</td> <td>1/27 (3.7%)</td> </tr> <tr> <td>HD-TGGE</td> <td>34/53 (64%)</td> <td>1/27 (3.7%)</td> </tr> <tr> <td>FA</td> <td>33/53 (62%)</td> <td>2/27 (7.4%)</td> </tr> </tbody> </table>		CTCL	Benign	HD-MDE PAGE	22/53 (41.5%)	1/27 (3.7%)	HD-TGGE	34/53 (64%)	1/27 (3.7%)	FA	33/53 (62%)	2/27 (7.4%)							
	CTCL	Benign																				
HD-MDE PAGE	22/53 (41.5%)	1/27 (3.7%)																				
HD-TGGE	34/53 (64%)	1/27 (3.7%)																				
FA	33/53 (62%)	2/27 (7.4%)																				
Signoretti et al. ⁶⁹	T-cell lymphomas (21), Reactive lymphocytic infiltrate (12), Primary cutaneous large BCL (2)	PCR-SSCP	Clonal TCR- γ GR found in skin of: 15/16 (93.8%) CTCL 0/6 (0%) reactive lymphoid infiltrate 0/2 (0%) large B-cell lymphoma	95% sensitivity in all T-cell lymphomas																		
Tang et al. ⁷⁰	MF (17), Non-MF CTCL (4), Lymphoblastic leukemia (1)	PCR-PAGE vs. PCR-FCE	Monoclonal TCR- γ GR found in: <table border="1"> <thead> <tr> <th></th> <th>PCR-PAGE</th> <th>PCR-FCE</th> </tr> </thead> <tbody> <tr> <td>MF</td> <td>11/17 (64.7%)</td> <td>14/17 (82.4%)</td> </tr> <tr> <td>Non-MF CTCL</td> <td>3/4 (75%)</td> <td>3/4 (75%)</td> </tr> <tr> <td>LL</td> <td>0/1 (0%)</td> <td>0/1 (0%)</td> </tr> </tbody> </table>		PCR-PAGE	PCR-FCE	MF	11/17 (64.7%)	14/17 (82.4%)	Non-MF CTCL	3/4 (75%)	3/4 (75%)	LL	0/1 (0%)	0/1 (0%)	Complete agreement in 19 cases (86.4%). Sensitivity: - PCR-FCE: 77.3% - PCR-PAGE: 63.6%						
	PCR-PAGE	PCR-FCE																				
MF	11/17 (64.7%)	14/17 (82.4%)																				
Non-MF CTCL	3/4 (75%)	3/4 (75%)																				
LL	0/1 (0%)	0/1 (0%)																				
Tok et al. ⁷¹	CTCL (39), Controls (16)	PCR/DGGE	Clonal TCR- γ GR found in: 73% of nondiagnostic (by H&E) for CTCL 71% of cases suggestive of CTCL 74% of cases diagnostic for CTCL 2/16 (12.5%) of controls	Clonal TCR- γ GR may be detected in early CTCL, even when histology findings are not diagnostic.																		
Wolff-Sneedorff et al. ⁷²	CTCL (22), Suspected CTCL (5), Benign (5)	Southern blot	Clonal TCR- β GR found in skin of: 0% of benign cutaneous conditions 100% of MF 100% (2/2) SS 60% (3/5) clinically suspected CTCL 50% (5/10) large cell lymphomas																			
Wood et al. ⁷³	MF/SS (68), Other lymphoid infiltrate (105)	PCR/DGGE vs. Southern blot	Clonal GR found in skin of: <table border="1"> <thead> <tr> <th></th> <th>TCR-γ by PCR/DGGE</th> <th>TCR-β by SB</th> </tr> </thead> <tbody> <tr> <td>MF/SS</td> <td>61/68 (90%)</td> <td>10/17 (59%)</td> </tr> <tr> <td>Non-MF/SS</td> <td>6/105 (5.7%)</td> <td>Not done</td> </tr> </tbody> </table>		TCR- γ by PCR/DGGE	TCR- β by SB	MF/SS	61/68 (90%)	10/17 (59%)	Non-MF/SS	6/105 (5.7%)	Not done										
	TCR- γ by PCR/DGGE	TCR- β by SB																				
MF/SS	61/68 (90%)	10/17 (59%)																				
Non-MF/SS	6/105 (5.7%)	Not done																				

CTCL, Cutaneous T cell lymphomas;

DGGE, denaturing gradient gel electrophoresis; FA, fragment analysis; GSA, GeneScan analysis; HD, heteroduplex; LL, lymphoblastic leukemia; LyP, lymphomatoid papulosis

MDE, mutation detection enhancement; MF, mycosis fungoides; ATL, adult T cell leukemia/lymphoma

PAGE, polyacrylamide gel electrophoresis; SS, Sézary syndrome

SSCP, single strand conformational polymorphism; TGGE, temperature gradient gel electrophoresis

TABLE 5-9—Summary of Cytogenetic Studies

Author(s)	Diagnoses	Findings
Barba, et al. ⁷⁴	3 MF 4 primary SS	Chromosomal imbalances in: <ul style="list-style-type: none"> • 100% (4/4) Sézary • 33% (1/3) MF • All 5 abnormalities had duplication at 17q; in 3/5 this = sole genomic event.
Batista, et al. ⁷⁵	19 blood samples from pts w/MF/ SS analyzed with cytogenetics & multicolor FISH (SKY)	47% (9/19) abnormal karyotype
Berger, et al. ⁷⁶	17 T-cell malignant lymphomas, including 6 CTCL	
Mao, et al. ²⁴	18 Sézary (37 DNA samples) 16 MF (22 DNA samples)	CGH showed chromosome imbalances in: <ul style="list-style-type: none"> • 56% (19/34) • 10/16 MF • 9/18 SS

CGH, comparative genomic hybridization; CTCL, cutaneous T cell lymphomas; MF, mycosis fungoïdes; Sézary syndrome.

CYTogenetic studies

Conventional cytogenetic studies are of limited use in primary cutaneous T-cell lymphomas, because of the low mitotic index of CTCL clones and poor morphology of their mitoses. Furthermore, in early stage mycosis fungoïdes, peripheral blood is often not involved; karyotyping of skin samples is difficult because the tumor cells are terminally differentiated and contaminated by large numbers of reactive cells. However, in patients with advanced CTCL, chromosomal abnormalities have been reported in peripheral blood lymphocytes.²⁴ Such karyotypic changes have been reported to be associated with a worse prognosis.²⁴ Table 5-9 summarizes the applicable studies.

PHENOTYPIC STUDIES

Flow cytometry may be used in cases that are difficult to interpret. A PubMed search was conducted on flow cytometry in the context of CTCLs. Table 5-10 summarizes the findings from some of the studies that have examined surface marker expression in mycosis fungoïdes and

TABLE 5-11—CD3^{dim} Expression in Mycosis Fungoïdes and Sézary Syndrome²⁵

	# of Patients	Source
MF/SS	4 of 4	Blood ± bone marrow or lymph node
MF/SS	2 of 2	Lymph node ± bone marrow
No evidence of MF/SS	0 of 14	Blood ± lymph node

MF, mycosis fungoïdes; Sézary syndrome.

anaplastic large cell lymphoma. The remainder of this section will focus on specific markers.

CD3

CD3 is a marker primarily restricted to T lymphocytes. Reduced expression of CD3 is often seen in T lymphocyte populations from blood, bone marrow, or lymph nodes in CTCL, MF-type or SS, and the use of the term “CD3^{dim}” to refer to T cell populations with reduced (but not absent) expression of CD3 has been proposed.²⁵ Table 5-11 summarizes the findings by Edelman and Meyerson. The use of CD3^{dim} versus CD3⁺CD7⁻ lymphocyte populations for the detection of MF/SS has also been studied. Patients without evidence of MF/SS averaged 5.5% CD3⁺CD7⁻ cells, suggesting that the use of CD3^{dim} may more accurately estimate the true number of circulating abnormal lymphocytes, in cases where there are not a lot of truly abnormal lymphocytes, as CD3⁺CD7⁻ lymphocytes may also be present in benign dermatoses^{25–27}.

CD4 & CD8

Altered expression of CD4 relative to CD8 can also occur in CTCL.²⁸ As noted in the introduction, the ISCL has proposed a CD4:CD8 ratio of greater than 10:1 as a criteria for SS.⁴ It has been suggested that a CD4:CD8 ratio greater than 10:1 occurs in between 60% to 80% of patients with SS.²⁹ One study has shown that SS patients do indeed have elevated CD4:CD8 ratios compared to those with MF, benign dermatoses, and unaffected individuals.³⁰ Table 5-12 summarizes these findings. In contrast, an earlier study investigated the CD4 and CD8 surface markers in the peripheral blood of patients with CTCL and found elevated CD4:CD8 ratios in patients with SS as well as MF (Table 5-13).³¹ Compared to normal controls and individuals with psoriasis, atopic dermatitis, or chronic dermatitis, the SS patients had CD4:CD8 ratios averaging 31.4, followed by the MF patients with ratios of 9.4.³¹ In contrast, patients with psoriasis,

TABLE 5-10—Summary of Phenotypic Findings by Flow^{30,32,77}

	CD2	CD3	CD4	CD5	CD7	CD8	CD26	CD30
MF	+	dim/+	+	+	-	-	-	-
ALCL	+++	++	-/++	+	++	+/-	—	+

TABLE 5-12—CD4:CD8 Ratios in Peripheral Blood are Elevated in Patients with Sézary Syndrome Compared to Patients with Mycosis Fungoides and Benign Dermatoses³⁰

	Mean CD4:CD8 Ratio	# of Patients
SS	21.5	28
MF	2.4	9
Benign Dermatosis	1.3	7
Control	3.3	12

MF, mycosis fungoides; SS, Sézary syndrome.

atopic dermatitis, or chronic dermatitis had CD4:CD8 ratios less than or equal to 3.1.³¹ These data suggest that individuals with CTCL have elevated CD4:CD8 ratios compared to other inflammatory diseases. The proposed criterion of a ratio of 10:1 is hence, in line with these findings.

CD7

CD7 loss has also been reported in patients with SS. One study noted a partial or complete loss of CD7 in 86 of 112 (76.8%) SS patients as the only aberration.³⁰ In another study, CD4⁺CD7⁻ cells were elevated in many SS/MF patients compared to normal controls.³² This study noted, however, that about a quarter of the patients with elevated CD4:CD8 ratios had CD7⁺ abnormal cells, suggesting that up to a quarter of such patients could be missed by relying on CD7 loss only.³² The authors also concluded that the lack of a large population of CD4⁺CD7⁻ cells in the context of a normal CD4:CD8 ratio is not diagnostically useful.³² A CD4⁺CD7⁻ cell population in the context of an elevated CD4:CD8 ratio would, therefore presumably be more useful in the diagnosis of MF/SS.³²

CD26

CD26 (dipeptidyl peptidase IV (DPP IV)) loss has also been proposed as a marker of MF/SS cells^{29,33}. In a recent study with 179 individuals, CD26 loss on peripheral blood

TABLE 5-14—CD26 Loss in Peripheral Blood in Patients with SS, MF, and Benign Dermatoses³⁰

	Percent CD26 negativity based on flow cytometry
SS	59.30%
MF	33.30%
Benign Dermatosis	14.20%

MF, mycosis fungoides; SS, Sézary syndrome.

lymphocytes was greater in SS versus MF versus benign dermatoses (Table 5-14).³⁰ Furthermore, another study looked at CD4⁺CD26⁻ cells in patients with MF, SS, erythrodermic inflammatory skin disorders, and normal controls.²⁹ In this study, the percent of CD4⁺CD26⁻ lymphocytes was higher than 30% in 13/14 of B1-MF patients.²⁹ The percent of CD4⁺CD26⁻ lymphocytes was higher than 40% in all SS cases.²⁹ However, all normal controls, individuals with erythrodermic inflammatory skin disorders, and individuals with B0-MF disease always had percentages lower than 30%.²⁹ Taken together, these two studies appear to support a cutoff around 30% for disease involving the blood. Of note, the first study discussed did not delineate between B0-MF and B1-MF, and hence, it is possible that any differences between the two subgroups of patients without MF with respect to CD26 were not appreciated, as was the case with the second study.

CLOSING

As depicted above, an accurate diagnosis of CTCL may be challenging. Multiple diagnostic modalities may be necessary to arrive at a definitive diagnosis. Although the diagnosis may be made, determining the full extent of disease and correct staging involves additional tests. Rosen et al. suggested the following tests in the initial evaluation of suspected CTCL: “CBC with differential, chemistry panel, LDH, skin biopsy for histopathology, immunophenotyping, and TCR gene analysis, blood smear for Sézary cell count, flow cytometry: T-cell subsets, CD4/CD8 ratio, TCR gene analysis (skin, blood, lymph node), lymph node biopsy of palpable nodes, imaging: CT/PET scans (chest, abdomen, pelvis), bone marrow biopsy, and serologic tests: HTLV-1, HIV”³⁴.

Keehn, et al. noted, “further clinical evaluation of CTCL patients includes a complete history and physical examination, emphasizing the types of skin lesions, body surface area, lymph node, liver, and spleen involvement. Baseline tests should include a complete blood cell count; additional tests that may be useful in staging patients with clinically advanced MF include peripheral blood flow cytometry for T-cell subsets, serum chemistries (liver and renal function tests, calcium, phosphorus, uric acid, and lactate dehydrogenase), chest radiograph, and biopsy of palpable lymph nodes. Staging procedures for patients with advanced disease would also include computed tomography (CT) scan of the neck, abdomen, and pelvis, and also

TABLE 5-13—CD4:CD8 Ratios in the Peripheral Blood of Patients with SS, MF, or Benign Dermatoses³¹

	CD4:CD8 Ratio (mean)	s.d.	# Patients
SS	31.4	24.1	8
MF	9.4	5.9	4
Atopic or Chronic Dermatitis	3.1	1.4	14
Psoriasis	2.2	0.5	6
Normal Controls	2.1	0.4	10

MF, mycosis fungoides; SS, Sézary syndrome.

What We Know

- Cutaneous T-cell lymphoma (CTCL) often presents with a spectrum of clinical signs and symptoms and can be difficult to diagnose because of similarities to more common inflammatory skin conditions.
- Evidence exists to improve the sensitivity and specificity of the diagnosis of CTCL, including scoring systems that are referenced and reviewed in this chapter.
- Clinically, persistent and/or progressive patches or thin plaques as well as at least two additional criteria are required. Lesions located in a non-photoexposed area, variation in lesion size or shape, or poikiloderma can be important.
- Histologically, a superficial lymphoid infiltrate along with epidermotropism in the absence of spongiosis, as well as atypical lymphocytes, are significant.
- T-cell receptor gene rearrangement studies, if positive, offer additional support for the diagnosis
- Flow cytometry/phenotypic analyses can be used, using specified criteria, to assist in the diagnosis.
- A total body skin exam with attention to subtle areas of dermatitis and/or pigment change, as well as an assessment of lymph nodes, is important for any patient with potential CTCL
- The biopsy specimens used for the diagnosis should be sent to a pathologist/lab that you trust to have experience and interest in the diagnosis, and clinical-pathologic correlation can be very important.
- Counseling patients and other caregivers about the somewhat complicated diagnostic criteria for CTCL can be helpful in helping them understand the need for getting appropriate studies as well as anticipating potential ambiguities or delays in the initial diagnosis.

possibly bone marrow biopsy.”³⁵ Data from Sibaud et al. argue against the need for bone marrow examination in MF and SS patients.³⁶

In the end, the evidence-based diagnosis of CTCL is complicated because there is no one “gold standard” for diagnosis, and there are multiple data points that have some level of subjectivity. Still, consensus groups have come up with criteria to assist the clinician and patient and we believe this chapter may provide additional material to help the interested reader further understand this topic.

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UH Case Medical Center, Cleveland, OH. J.D.B. is from the Department of Dermatology, Case Western Reserve University. S.B.O. is from Pritzker School of Medicine, University of Chicago, Chicago, IL. E.S.M. is from the Division of Dermatology, Department of Medicine, Northeast Ohio Universities Colleges of Medicine and Pharmacy, Rootstown, OH. ”

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Diagnostic Criteria for Cutaneous Lupus Erythematosus

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INTRODUCTION

Lupus erythematosus (LE) is a systemic autoimmune disorder associated with polyclonal B cell activation that has heterogeneous clinical expression. The skin is a frequent target organ. The term “LE related skin disease” is generally used in a broad fashion to represent the many different types of cutaneous lesions that occur in LE patients. Cutaneous LE refers specifically to the forms of skin disease that are unique to lupus patients and share common histologic features.

Patients that present with cutaneous manifestations of lupus are best understood as existing along a spectrum of disease from no apparent systemic involvement (skin only lupus) to severe life-threatening systemic disease. Recent epidemiologic evidence suggests that patients with cutaneous LE that fail to meet criteria for systemic LE are at least as prevalent as those designated as having systemic LE.¹

Historically, cutaneous findings were the hallmark of LE and presently they remain a key component for several reasons. Skin changes may be the initial, or most easily recognized, feature of a disease that can target vital internal organs. In addition, untreated or undertreated skin disease may lead to erythema, dyspigmentation, and scarring in cosmetically sensitive areas.² The ability to make a correct and timely diagnosis of cutaneous LE, therefore, is crucial in terms of the ongoing evaluation and treatment.

The diagnosis of cutaneous LE is not always straightforward. Clinicians and specifically dermatologists are at times confronted with patients that seemingly have nonspecific skin lesions that may be photo-exacerbated along with nonspecific systemic complaints. Complicating this is the fact that many rheumatic diseases like LE can evolve over time and may not initially present in “full bloom.” Because of the heterogeneity of cutaneous LE the diagnosis of lupus is frequently entertained when creating a complete differential diagnosis. While clinical gestalt may be helpful, clinicians increasingly recognize the preference for a more evidence-based approach in making the diagnosis. In this scenario, the following research questions among others could be asked:

Research Questions

1. Are there established diagnostic criteria for cutaneous LE?
2. What clinical features or diagnostic tests are most helpful to establish a diagnosis of cutaneous LE?
3. What evidence, if any, is published about the predictive value of these tests?
4. How specific are certain histologic features for cutaneous lupus?
5. Is there reliable testing to distinguish different subtypes of cutaneous LE?

For a variety of reasons, evidence-based trials in all aspects of cutaneous LE have been at best sparse. The level of evidence for the majority of what will be discussed in this chapter comes from combined clinical experience from “experts” in the field. While there has been much discussion, and some attempt, to create evidence-based diagnostic criteria for cutaneous LE³, none have been validated in larger studies. Therefore, there is no single clinical feature or test that absolutely “clinches” the diagnosis of cutaneous LE. In the absence of validated criteria, cutaneous LE remains a clinical diagnosis correlated with the presence of characteristic histologic features seen in affected skin. For example, serologic (such as an ANA test) or immunofluorescence testing are often employed to strengthen, but are not strictly required for diagnosis.

The purpose of this chapter will be to review the published evidence regarding the diagnostic evaluation of cutaneous LE from a clinical, histologic, and laboratory standpoint. This should allow the clinician an understanding of the level of evidence available for different diagnostic methods. This chapter will focus on the diagnosis of cutaneous LE and not the relationship between cutaneous LE and systemic disease, nor any predictive testing in that regard.

CLINICAL FEATURES OF CUTANEOUS LE

The ability to make a diagnosis of cutaneous LE by definition requires the presence at some point in time of an

active skin lesion created by local autoimmune activation. While this statement seems obvious, the reader must remember that LE can and does manifest without cutaneous involvement. In addition, patients with LE can develop skin disease that may not be directly related to their underlying disease process.

As mentioned, the clinical features of cutaneous LE are variable and different presentations have been identified with an increased risk of scarring or with an increased likelihood of internal disease.⁴ The idea of a classification system for LE-related skin disease was recognized. The method and terms used have been debated over the years. For the purposes of the remainder of this chapter we will use the well recognized Gilliam classification to discuss the diagnostic approach to each subtype.⁵ (Table 6-1) As part of this classification, LE-related skin disease is divided into two broad categories: lupus-specific and lupus nonspecific skin disease. Lupus erythematosus (LE)-specific skin disease refers to those lesions that have the characteristic histologic changes of LE, which will be discussed later in this chapter. LE nonspecific skin disease refers to those cutaneous lesions that are related to the patient's underlying autoimmune disease but do not share the characteristic histologic features of LE (e.g., cutaneous vasculitis).

TABLE 6-1—Gilliam Classification of Lupus Erythematosus (LE) Associated Skin Lesions

LE- specific skin lesions
Acute cutaneous LE
Localized
Generalized
Subacute cutaneous LE
Annular
Papulosquamous
Chronic cutaneous LE
"Classic" Discoid LE
Localized
Generalized
Lupus Panniculitis
Mucosal LE
Hypertrophic discoid LE
Chilblains LE
Discoid LE-lichen planus overlap
LE- non specific skin lesions
Vasculitis
Vasculopathy
Alopecia (non-scarring)
Urticaria
LE-non specific bullous lesions
Others

(Adapted from Costner MI.⁴)

Lupus erythematosus-specific skin disease is further divided into three broad categories based on clinical and histologic features. Acute cutaneous lupus (ACLE), subacute cutaneous lupus (SCLE) and chronic cutaneous lupus (CCLE).⁶ These subtypes are associated with different patterns of risk for systemic LE disease activity. There is considerable variability in terms of cutaneous presentation within each of these groups. Some cutaneous LE patients may manifest more than one type of cutaneous LE or have skin lesions that are indeterminate (don't fit well into any category).

ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (ACLE)

The localized form of ACLE has classically been termed a "malar rash" or "butterfly rash". This refers to the confluent symmetric erythema that occurs over the malar eminences and bridge of the nose and sparing the nasolabial folds. It carries a strong association with systemic disease and if present qualifies as one of the 11 American College of Rheumatology (ACR) classification criteria for systemic LE.⁷ (It is important to understand that these ACR criteria were developed for the classification of SLE for the purposes of clinical research studies. They were not intended to serve as diagnostic criteria in clinical settings.) In large cohorts, it is a feature in 20–60% of patient with systemic LE.⁸ Rather than confluent erythema, the eruption may begin as erythematous papules in a similar distribution. There is also a more generalized variety that may occur as a morbilliform or exanthematous eruption on the trunk and extremities.

The diagnosis of ACLE based on the above features is often made without a biopsy. However, there are many other causes of malar erythema that have been reported as clinical mimics of ACLE including rosacea, tinea facie, dermatomyositis, photodrug reaction, polymorphous light eruption, acute graft-versus-host disease, cutaneous tuberculosis, and leishmaniasis. There are currently no evidence-based systematic studies that clinically differentiate among these differential diagnosis entities.

Rosacea deserves special mention as a clinical mimicker of ACLE. In a study of patients referred to a dermatology clinic for treatment with a presumptive diagnosis of LE, there were 21 (6.7%) who were in fact diagnosed as having a different dermatologic condition. Of these, 16/21 (76%) had rosacea based on biopsy and/or clinical features. Many of these patients did have at some point, low positive ANA titers. This would suggest that at times rosacea can be difficult to clinically differentiate from ACLE and clinicians may give too much weight to serologic testing.⁹

SUB-ACUTE CUTANEOUS LUPUS ERYTHEMATOSUS (SCLE)

SCLE consists of nonscarring papulosquamous or annular skin lesions that occur in a characteristic photo-distribution.

These two morphologies can appear together in the same patient and appear to have a similar prevalence in case series. Interestingly SCLE usually spares the central face. The individual annular lesions often have an active border that can demonstrate vesiculation and crusting. While SCLE does not scar it can result in marked “vitiligo-like” hypopigmentation. Photosensitivity is a common feature of SCLE, occurring in 85% of patients.^{10–11}

The clinical differential diagnosis for SCLE includes psoriasis, drug eruptions, actinic granuloma annulare, erythema multiforme, and other forms of cutaneous lupus. There are again few studies that have attempted to differentiate SCLE from other dermatologic conditions based on clinical features. However, there are a few comparisons of the clinical features of SCLE compared to CCLE. In one study, a comparison of the clinical, histologic, and immunofluorescent distinctions between SCLE and CCLE in 27 patients was performed.¹² Clinical features most characteristic of SCLE rather than DLE included superficial, nonindurated, nonscarring lesions, and photosensitivity. The lack of induration of an active lesion was the single most helpful finding to clinically distinguish SCLE from CCLE.

When evaluating a patient with suspected SCLE, approximately half of patients will meet four ACR criteria for SLE but only 10–15% of SCLE patients will develop severe manifestations of SLE (i.e., lupus nephritis).¹¹ The presence of double-stranded DNA antibodies and overlapping cutaneous features of ACLE could also indicate a higher risk for clinically significant systemic LE disease activity and damage in a SCLE patient. SCLE can also overlap with other autoimmune disorders, particularly Sjögren's syndrome.¹³

In 1985, Reed and coworkers reported five patients who had not previously experienced features of SLE or cutaneous LE who developed clinically, histopathologically, and immunopathologically typical SCLE skin lesions while taking hydrochlorothiazide.¹⁴ Since that time over 100 cases of suspected drug-induced SCLE have been published.¹⁵ The list of associated medications continues to grow but common culprits include antihypertensive agents and oral terbinafine.¹⁶ At this time, there are no biologic markers to reliably distinguish drug- induced from idiopathic SCLE. The diagnosis is made with clinical suspicion and resolution of the condition upon withdrawal of the medication. In the appropriate clinical setting drug-induced SCLE should be considered, particularly in patients with onset over 50 years of age.

CHRONIC CUTANEOUS LUPUS ERYTHEMATOSUS (CCLE)

Chronic cutaneous lupus erythematosus refers to cutaneous LE lesions that differ clinically from SCLE and ACLE in their propensity to be chronic and scarring. In the spectrum of CCLE are entities such as discoid LE, chilblain LE, and LE panniculitis/LE profundus. For the purposes of this chapter, only discoid LE lesions will be discussed.

The most common form of CCLE is termed “classic” discoid LE. “Classic” discoid LE lesions typically begin as red-purple macules that over time usually evolve into larger, coin shaped plaques with prominent, adherent scale extending into hair follicles. Eventually the lesions tend to develop central scarring and depigmentation. In more darkly pigmented individuals, characteristic postinflammatory disturbances are seen—hyperpigmentation at the active borders and hypopigmentation at the inactive centers. The most typical areas of involvement include the face, scalp, and ears. Some patients will develop more disseminated lesions on the upper trunk, extensor arms, and even legs. It has been verified in larger cohorts that discoid lesions rarely occur solely below the neck. There are less common clinical variations of discoid lesions that include hypertrophic discoid LE, mucosal discoid LE, and discoid LE/lichen planus overlap.

The differential diagnosis for discoid LE lesions is large and depends on the stage of development and location. Early lesions may be clinically similar to tinea, sarcoid, contact dermatitis, seborrheic dermatitis, lichen planus, or psoriasis. More advanced lesions may resemble nonmelanoma skin cancers, hypertrophic lichen planus, scarring infectious processes such as tuberculosis or leishmaniasis, or even depigmenting conditions such as vitiligo or morphea. One useful clinical feature that is often present in more advanced discoid lesions is follicle-sized keratotic spikes sometimes referred to as “carpet tacks.” Whether this is a true pathognomonic feature of discoid lesions has not been studied.

IMMUNOHISTOLOGIC FEATURES OF CUTANEOUS LE

Histologic examination is critical in establishing a diagnosis of cutaneous LE. Like most inflammatory conditions in the skin, there is no single histologic feature that is diagnostic for LE. “LE specific histology”, as previously discussed, does not imply that the characteristic histologic changes seen in LE-specific skin disease may absolutely not be seen in any other cutaneous disease process. It is a term that allows clinicians to classify types of cutaneous lesions commonly seen in LE patients. LE-specific skin disease is characterized by a lymphocytic vacuolar interface dermatitis.¹⁷ The intensity of the infiltrate and additional histologic features can vary. The capacity to distinguish among the different types of LE specific skin disease based on histologic features is more controversial. Attempts have been made to determine to what degree specific histologic features associate with specific subtypes of cutaneous LE. Features such as: epidermal atrophy, hyperkeratosis, follicular plugging, and mucin deposition have been examined. The ability of a blinded dermatopathologist in two different studies to correctly identify the correct clinical subtype of cutaneous LE based on histologic features alone is quantified in Table 6-2.^{18–19} These data would suggest that histologic differentiation of

TABLE 6-2—Clinical/Histopathologic Correlation of Subsets of Cutaneous Lupus

	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
CCLE (n=66)	64%	67%	72%	57%
SCLE (n=48)	54%	74%	60%	69%

N=114, CCLE- Chronic cutaneous lupus erythematosus, SCLE- Subacute cutaneous lupus erythematosus.

clinical subtypes of cutaneous LE is not reliable based on the features examined in these studies.

In addition to routine histology, immunopathology has been employed for several decades for the diagnosis of cutaneous LE. The test has been used both to aid in the diagnoses of cutaneous LE by sampling lesional skin and at times to assess risk for systemic LE disease activity by seeking to identify immunoreactants (IgG, IgM, IgA, and/or C3) displayed in a band-like fashion at the dermal-epidermal junction of nonlesional skin (i.e., “lupus band test”). This chapter will focus on immunopathology in lesional skin to assist the diagnosis of cutaneous LE and not systemic disease.

The usefulness of direct immunofluorescence microscopy in the diagnosis of cutaneous LE has been debated. The chief problem being that similar patterns of immunoreactants have been reported in lesional skin from many conditions including dermatomyositis, porphyrias, granuloma annulare, necrobiosis lipoidica diabetorum, amyloidosis, graft versus host disease, psoriasis, pyoderma gangrenosum, sarcoidosis, leprosy, erythema multiforme, scabies, facial telangiectasias, and pemphigoid.²⁰ In addition, actinically damaged skin can also produce false positive findings that can be confusing. This calls into question the clinical utility of the test.

In order to gain a sense for the diagnostic utility of direct IF testing to diagnose cutaneous lupus, Table 6-3 characterizes the sensitivity of immunofluorescent (IF) testing in different dermatologic conditions based on a portion of a larger study from the Warsaw Academy of Medicine.²⁰ It has been argued that while false positives are common, the density and pattern of the immunodeposits and the presence of multiple immunoreactants can increase the positive predictive value.²¹ This claim has not been objectively quantified and what constitutes a dense immunodeposit is still somewhat subjective.

Histology of Acute Cutaneous Lupus Erythematosus

The histology from the common macular form of ACLE is often subtle and nonspecific. Along the dermal-epidermal junction, vaculopathic degeneration of keratinocytes can be seen.¹⁷ In severe pronounced cases, there may be frank epidermal necrosis resembling toxic epidermal necrolysis.²² More commonly, there is typically a sparse dermal cellular

infiltrate with variable edema. The presence of increased dermal mucin has long been recognized as a key histologic feature in cutaneous lupus. These mucin deposits can be stained with colloidal iron or Alcian blue preparations. Some experts feel this is the most useful morphologic finding to favor a diagnosis of LE over other causes of a lichenoid interface dermatitis.¹⁷ However, there have not been quantitative studies published to determine if increased mucin is seen in all biopsies or to what degree.

The major histologic differential diagnosis for ACLE is dermatomyositis (DM). A blinded study looked at the cutaneous pathologic changes of DM versus ACLE in 20 biopsy specimens from lesions matched for anatomic site and lesion morphology.²³ When given those two options, investigators were only able to make the correct histopathologic diagnosis of DM or ACLE in 11 of the 20 cases, suggesting that ACLE cannot be distinguished from DM based solely on histology.

There are few published data on the direct immunofluorescence findings in ACLE. Most of the published studies deal either with nonlesional skin or with lesional skin in CCLE or SCLE. There are also little data on specific patterns in these lesions. The age and location of the skin lesion as related to sun exposure influence the prevalence of such deposits.

Histology of Subacute Cutaneous Erythematosus

Histology of SCLE also shows interface dermatitis with variable degrees of hyperkeratosis, basal cell degeneration,

TABLE 6-3—Diagnostic Testing for Cutaneous LE- Immunofluorescence

Diagnosis	Sensitivity of IF testing (%)
Discoid lupus erythematosus	79
Polymorphous light eruption	17
Rosacea	51
Lichen Planus	66
Telangiectasias	36
Porphyrias	40
Pemphigus erythematosus	81
Vasculitis	8

(Adapted from Dahl MV²⁰).

dermal edema, and mononuclear cell infiltration around the dermal-epidermal junction extending into the dermis. The mononuclear infiltrate is usually limited to perivascular and adnexal structures in the upper third of the dermis, and the epidermis may be mildly atrophic. There is considerable overlap in the features of SCLE versus “classic” discoid lesions, as mentioned. The data to this point would indicate that while there are histologic features that would favor a diagnosis of discoid LE over SCLE, there is enough overlap to state that the two subtypes cannot be completely differentiated from the histology.²⁴ No attempts have been made to take into account the age of the lesion biopsied with the hypothesis being that an advanced discoid lesion is more likely to appear considerably different from SCLE.

In the original cohort of patients with SCLE, approximately 60% were found to have deposits consisting of immunoglobulin and complement components arranged in a granular bandlike pattern along the dermal-epidermal junction in lesional skin.²⁵ Later studies have confirmed this number or found greater frequencies.²⁶ Some investigators have reported the presence of a dust-like pattern of IgG deposition over the dermal-epidermal junction and epidermal basal layer to be enriched in SCLE lesions compared to other forms of LE-specific skin disease.²⁷ This immunofluorescence pattern appears to correlate with the presence of Ro/SS-A autoantibodies in the circulation. The presence of immune deposits in lesional skin from a patient suspected of having SCLE can help confirm the diagnosis, but its absence does not necessarily rule it out. It is worth remembering that these deposits are not specific for LE as they can be seen in normal and particularly sun-exposed skin, and may be present in other non-LE dermatologic conditions and therefore must be correlated to the routine histopathology.

LABORATORY FINDINGS

Chronic Cutaneous Lupus Erythematosus

Discoid lesions are characterized by an interface dermatitis that involves the hair follicles and epidermis. Such lesions typically have a more intense superficial and deep perivascular and periappendageal lymphocytic infiltrate. There is often marked hyperkeratosis with keratotic follicular plugging. Acanthosis and dermal fibroplasia can be seen in older lesions.

As in other subtypes, direct immunofluorescence microscopy is frequently positive at the dermal-epidermal junction in discoid LE lesions. The exact percentage varies in different reports but may be as high as 90%.²⁸ One study took 28 patients with CCLE and compared them to 15 controls with lesions that clinically simulated CCLE in some fashion. Histopathologic examinations and direct immunofluorescence was performed on lesional skin from all sets of patients. The immunofluorescent testing revealed

a sensitivity of 58% and specificity was 87% with a positive predictive value of 95% and a negative predictive value of 32%.²⁹ This study suggests that in patients presenting with discoid LE appearing skin lesions, a negative immunofluorescence would be useful in excluding discoid LE mimics. However, the study did not examine whether there was any added negative predictive value in comparison to routine histology alone.

There is no direct comparison of the type and morphology of the immunoreactant in chronic cutaneous LE in comparison to other forms of cutaneous LE. Expert opinion indicates that CCLE is unique in that the band of immunoreactants is generally thicker and extends along the basement membrane of the hair follicle. Additional studies have suggested that the frequency of immunoreactants can vary with anatomic location with the head, neck and arms often positive and the trunk often negative.³⁰ These locations correlate with increased exposure to UV light. The frequency may also be related to the age of the lesion with lesions older than 3 months being more often positive than newer lesions. A discussion of the histologic and immunologic features of other forms of CCLE such as lupus panniculitis is beyond the scope of this chapter.

LABORATORY FEATURES OF CUTANEOUS LE

As previously mentioned, the diagnosis of cutaneous LE is made on clinical grounds supported by characteristic histologic findings. Therefore, the purpose of any additional laboratory testing is two-fold:

1. To support the clinical and histologic diagnosis of cutaneous lupus
2. To establish the likelihood of systemic LE

This section will discuss the value of laboratory tests to support the diagnosis of the different subsets of cutaneous LE. Many of the laboratory tests used in the diagnosis of LE revolve around autoantibody testing. The interpretation of antibody testing, including the anti-nuclear antibody (ANA) test, can be complicated. The clinician interpreting the test must consider differences in techniques, patient age, comorbidities, and medications. One must also consider what result or level constitutes a significantly abnormal test. The astute clinician will therefore consider all these factors when applying the results of a specific autoantibody test result to a particular patient suspected of having cutaneous LE. The prevalence of particular serologies in subsets of cutaneous LE has generally been obtained through case series with variable results.

Acute Cutaneous Lupus Erythematosus

As ACLE is usually associated with systemic LE, laboratory profiles are similar. Antinuclear antibody testing remains

a very sensitive test for systemic LE with 99% prevalence.³¹ The 1% of “ANA-negative” systemic LE patients can typically be found to have Ro/SS-A autoantibodies upon investigation. The prevalence of ANA in patients presented with ACLE has not been directly measured but would one would expect it to closely parallel systemic LE. More specific but less sensitive tests include dsDNA, Sm, and rRNP autoantibodies. Hematologic abnormalities and proteinuria are frequently seen in systemic LE but are not necessarily related to the presence or diagnosis of ACLE.

Subacute Cutaneous Lupus Erythematosus

Antinuclear antibodies are detected in approximately 50% of patients with SCLE. Ro/SS-A antibodies are present in frequencies ranging from 40–100% of such patients. La/SS-B antibodies are present in 12–42% of patients with SCLE. Higher percentages are obtained for Ro/SS-A and La/SS-B antibodies, using the more sensitive enzyme-linked immunosorbent assay (ELISA).⁴ Ro/SS-A and La/SS-B antibodies have been repeatedly found to be more common in SCLE than in other forms of cutaneous LE. Sm, dsDNA, and U1RNP antibodies have been reported to occur in approximately 10% of patients with SCLE and can be indicators of clinically-significant underlying systemic LE.¹¹

Approximately 50% of patients with SCLE skin lesions will meet at least four criteria for systemic lupus.²⁵ Multiple laboratory abnormalities can again be seen including depressed complement levels, particularly in patients with systemic disease. These abnormalities are not specific to making a diagnosis of SCLE.

What We Know

- There are no validated diagnostic criteria for cutaneous LE.
- The diagnosis is made based on clinical findings supported by characteristic histopathologic features from an active skin lesion.
- Specific histopathologic features are variably present depending on the stage of the lesion biopsied.

Chronic Cutaneous Lupus Erythematosus

Laboratory findings in patients with CCLE, other than histopathology, are often of minimal use from a diagnostic standpoint. Patients with CCLE without systemic disease frequently have no detectable laboratory abnormalities.³² ANAs are detected in approximately 30% of these patients but are typically low titer.³³ Ro antibodies are found in approximately a quarter of patients with CCLE and U1RNP in perhaps 10%. Sm, La antibodies appear to be very uncommon in CCLE patients.⁴

Up to 25% of patients with SLE will develop discoid LE lesions at some point during the course of the disease.^{34–35} This group will clearly have different laboratory findings than those presenting with isolated CCLE.

CONCLUSION

The diagnosis of cutaneous LE is currently made by the presence of characteristic clinical features supported by the histopathology. There are currently no defined diagnostic criteria using clinical or histologic features that are supported by evidence-based medicine. One would anticipate that the development of reliable criteria could be very difficult for such a heterogeneous condition but if available, could be helpful in difficult cases.

Dermatologists frequently encounter patients with skin lesions in which they consider cutaneous LE to be in the differential diagnosis. If the clinical and histologic features still leave doubt, then there are tests that can be performed that may provide additional diagnostic information. These include direct immunofluorescence and autoantibody testing. The predictive value of these tests has been established in relatively small randomized studies.

- There is considerable histologic overlap between different clinical subsets of cutaneous LE.
- There are relatively few studies evaluating the predictive value of additional testing including immunofluorescence.

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Diagnosis of Parasitic Skin Diseases

7

Hermann Feldmeier, M.D.

SEARCH METHODOLOGY

Data for this chapter were found through searches of Medline and Lilacs databases using the keywords “pediculosis capitis”, “scabies”, “tungiasis”, and “cutaneous larva migrans” in combination with “diagnosis”. Additionally, reference lists of retrieved articles were searched. No date restrictions were set in these searches. Articles in English, French, German, Spanish, and Portuguese were analyzed. References found in text books on parasitic skin diseases, and tropical medicine were also used.

INTRODUCTION

In the past, the diagnosis of the four major parasitic skin diseases – scabies, pediculosis capitis, cutaneous larva migrans and tungiasis – essentially was based on clinical findings together with a history of exposure. However, clinical findings are seldomly specific and are subject to considerable inter-patient variation. Signs and symptoms depend on the duration of the infestation and its intensity, vary according to the developmental stage of the parasite, may be influenced by the age of the patient, and are modulated by a concurrent skin disease of non-infectious origin. This underlines the importance of diagnostic tools to identify the parasite in question, either directly on/in the skin or in ex vivo specimens.

Obviously, the suitability of diagnostic methods depends on the setting in which the patient lives. For instance, in areas where scabies is endemic – resource-poor communities and marginalized population groups - cost-intensive diagnostics requiring skilled personnel, such as videodermatoscopy, are not at hand and simple procedures have to be used instead. Therefore this chapter summarizes evidence on the validity of diagnostic approaches suitable in affluent or in resource-poor settings.

PEDICULOSIS CAPITIS

Parasite and life cycle/Epidemiology

Pediculus humanus capitis can only propagate on human scalp. From hatching of juvenile head lice to the next generation of eggs glued to hair shafts it takes 9 to 11 days. Head lice undergo only an incomplete metamorphosis, i. e.

juvenile lice are smaller than adult lice but have the same morphology. Transmission of head lice requires intimate head-to-head contact. Transmission through fomites is theoretically possible, but has little relevance in practice.

Clinical findings

Itching of the scalp is the most common symptom of head lice infestation. The degree of itching increases with the duration of infestation and the number of lice present on the scalp. However, whether this symptom is perceived or not seems to depend on the socio-cultural setting in which the patient lives. Whereas in Israel 30% of children infested with head lice complained about prurigo, in Venezuelan children only 14% reported this symptom^{1,2}.

Primary signs are reddish, intensively itching papules of 2-3 mm diameter. They are often surrounded by an erythema. Immediately after a bite wheals may occur, with the subsequent development of papules and itching. In the case of a primary infestation, signs develop with a delay of 4-6 weeks. This means that in the early phase of head lice infestation (when the patient is already infectious) the diagnosis cannot be made on clinical grounds. In the case of re-infestation, signs appear within 24-48 hours - an indicator for an immune-mediated reaction against components of lice saliva.

Secondary signs are the result of extensive scratching. Repeated scratching leads to **excoriations**. If the patient is not treated and continues scratching, an **ulcer** may develop. Excoriations reduce the natural barrier function of the epidermis and are an entry port for pathogenic microorganisms, typically *Staphylococcus aureus* and streptococci, leading to impetiginization of the scalp. The frequency of superinfection depends on the setting. In two resource-poor communities in Brazil, bacterial superinfection was observed in about 3% of infested individuals, while in France, only 1.2% of children with pediculosis capitis showed signs of superinfection^{3,4}.

Persistent superinfection leads to the development of regional lymphadenopathy. In two populations in Brazil with more than 10 episodes of head lice infestation per year and a restricted access to health care, cervical lymphadenopathy was observed in 12% and 15% of the infested individuals⁴. In children infested only temporarily, the

frequency of regional lymphadenopathy was similar to that of non-infested individuals⁵. Chronic infestations and persistent scratching may lead to eczema of the scalp (“lice eczema”). In homeless children or children refugees in low income countries, chronic impetiginization of the scalp associated with massive exsudation results in hair shafts intricately glued to each other (similar to the Polish plait observed in the 19th century).

Case history/Travel history

In western Europe the incidence of head lice infestation varies considerably during the year with a peak between calendar week 30 and 40, i. e. after the summer holidays⁶. Hence, in a child recent holidays support a presumptive diagnosis of pediculosis capitis.

Detection of parasites

Active pediculosis capitis – defined as the presence of nymphs, adults and/or viable ova – requires treatment. Presence of **only** egg shells (nits) or apparently dead ova is no indication for treatment. In praxis, though, it is not easy to make the differentiation between an active infestation and an infestation experienced in the recent past.

There are two methods to confirm the presence of *Pediculus humanus capitis* on human scalp: visual inspection and diagnostic combing (Table 7-1). In clinical practice the diagnosis of an active infestation is usually made by visual inspection, i.e. the direct observation of juvenile or adult head lice on the scalp. After parting the hair (e.g. with an applicator stick), the scalp is examined systematically, preferably with an illuminated magnifying glass (Figure 7-1).

Detection combing can be performed on dry or wet hair. Combs must have parallel-sided teeth and a distance



FIGURE 7-1 Visual inspection of the scalp and the hair using an applicator stick.

of ≤ 0.3 mm between teeth, so that the even juvenile lice are caught between the teeth. In wet combing a conditioner is applied onto the hair first. When coated by the conditioner, lice cannot crawl away, stick to the comb and are easily detected in the conditioner liquid. After each strike, the conditioner is wiped on sanitary paper and objects stuck between the teeth of the comb are inspected (Figure 7-2 A,B,C). Combing has to be done systematically from one side of the head to the other until the first louse is detected. If the entire hair is combed, diagnostic combing has the additional benefit of treatment.

Several authors have tried to determine the accuracy of visual inspection and wet combing. In one study, in only 6% of children head lice were found on the scalp by visual inspection, as compared to 25% after detection combing, resulting in a sensitivity of visual inspection of 22%. More recent data from a study in Turkey revealed a sensitivity of

TABLE 7-1—Diagnostic Value of Visual Inspection Versus Wet Combing

A) Presence of eggs/nits Diagnostic parameter	Visual inspection % (95% CI)	Wet combing % (95% CI)
Sensitivity	86.1 (82.2 – 90.0)	68.4 (63.1 – 73.7)
Positive predictive value	100	100
Negative predictive value	95.3 (92.9 – 97.7)	89.8 (86.5 – 93.1)
Accuracy	96.3 (94.1 – 98.5)	92.0 (88.9 – 95.1)
B) Presence mobile stages		
Sensitivity	28.6 (23.5 – 33.7)	90.5 (87.2 – 93.8)
Positive predictive value	100	100
Negative predictive value	94.9 (92.4 – 97.4)	99.3 (98.3 – 100.0)
Accuracy	95.0 (92.5 – 97.5)	99.3 (98.3 – 100.0)

Source: Adapted from Jahnke et al.; Archives of Dermatology 2009; 145:309–313.



FIGURE 7-2 Wet combing for detection of active pediculosis capitis. The hair is extensively wetted with conditioner (A) and then systematically combed with a high quality lice comb (B). After each strike the comb is wiped on a piece of white sanitary paper (C).

31%. In an observer-blinded, prospective diagnostic trial Jahnke et al.⁹ differentiated the diagnostic value of visual inspection and wet combing with regard to the detection of immobile and mobile stages. The authors showed that the sensitivity of visual inspection in detecting eggs/nits was significantly better than wet combing (86% versus 68%; P<0.001). The negative predictive value of visual inspection was also better (95.3% versus 89.8%; p<0.01). In contrast, wet combing largely outperformed visual inspection in the diagnosis of trophic stages: sensitivity 90.5% versus 28.6%, respectively (p<0.001); negative predictive value 99.3% versus 94.9%, respectively; (P<0.01). If only visual inspection was used, the true prevalence of active infestation would have been underestimated by a factor of 3.5.

In industrialized countries children have rarely more than 10 head lice¹⁰. This is important, because the sensitivity of any diagnostic method for parasitic skin diseases depends on the intensity of infestation. For instance, in patients with ≤10 trophic stages the sensitivity of wet combing is in the order of 90%, in patients with 20 head lice or more it is considered to be 100%⁵.

If in a scientific investigation the intensity of infestation needs to be determined, the number of head lice detected during the first three (or five) minutes of wet combing is a good proxy¹¹.

As head lice cannot be confounded with artefacts, theoretically the specificity of visual inspection and of detection combing should be very high. However, diagnosis of head lice infestations is often done by people who are not familiar with the size and the shape of head lice and their eggs and misinterpret what they see. In the USA, only 59% of 614 samples sent to a reference centre contained trophic forms or eggs¹². Surprisingly, only 17% of samples forwarded by physicians contained louse-derived material, as compared to 70% from nurses and 86% from teachers¹². Debris such as dandruff, and other epidermal material was found in 35% of all samples, other arthropods (book lice, beetles mites, bed bugs etc.) in 5%. In addition, only 53% of the specimens thought to contain a trophic stage or a viable egg actually showed the corresponding life stages of the parasite. Hence, reports by lay people and physicians on the presence of head lice should be interpreted with caution.

Resource-poor setting

In resource-poor settings a very simple approach to diagnose head lice infestation is asking individuals about their infestation status. Caretakers in poor communities in Brazil and Nigeria, after being asked about the presence of head lice on the head of their children, were aware of the infestation status with a sensitivity of 74% - 81% for active infestation^{13,14}. In the case of severe infestation, the sensitivity of self-diagnosis was as high as 92%.

Laboratory investigations

Head lice and their eggs are easily identified in a dissecting microscope. Haematological examinations are not helpful.

SCABIES

Parasite and life-cycle/Epidemiology

Sarcoptes scabiei is an arachnid of the genus *Acarus*. Humans are the only host of *Sarcoptes scabiei var. hominis*. Sarcoptes mites from companion animals only temporarily infest human skin. The female mite is responsible for symptoms and signs. Fertile females burrow into the stratum corneum of the epidermis, where they feed and produce ova. They live four to six weeks, producing two to four eggs per day which are deposited in the burrow. After two to four days larvae hatch from the eggs, and the next generation of adults develops within 10 to 14 days.

During a few months parasites accumulate in the skin, but then decrease in number over time - partly due to protective immune responses of the host, partly because scratching destroys burrows and thereby eliminates mites. On the average not more than 10 mites are present after six months of infestation¹⁵.

Transmission of mites requires prolonged intimate body contact, such between mother and her child, or during sexual intercourse. Mites can also be transmitted through contaminated fomites, however, the importance of inanimate reservoirs is usually overestimated by the patient. Off-host survival depends on temperature and humidity¹⁶.

In primary infestations, the incubation time is 3 to 6 weeks. Reinfestation is associated with a brisk immune response and an onset of symptoms within 24 to 72 hours.

General remarks

Currently, there is no satisfactory method of diagnosing scabies. Usually, diagnosis is made via clinical signs and microscopic examination of skin scrapings, but experience has shown that the sensitivity of these approaches is less than 50%¹⁷. Detecting visible lesions can be difficult, as they are often obscured by impetigo or eczema or are atypical. Given the many differential diagnoses, the specificity of clinical

diagnosis is poor. Furthermore, there is a problem in distinguishing among active infestation, residual skin reaction, and reinfestation. A presumptive diagnosis can be made on the basis of a local intense pruritus, pruritus that is worse at night, the topographic localization of the suspicious lesion, and a history of contact with other scabies cases.

Clinical findings

Scabies can mimic a broad range of skin diseases (Table 7-2). When a patient uses cosmetics extensively, typical appearances may be absent ("scabies incognito"). The systemic or topical administration of corticosteroids – even if only for a couple of weeks – also masks the clinical picture.

Clinical appearances are differentiated into **primary** (macules, papules, vesicles, burrows, nodules) and **secondary lesions** (crusts, excoriation, eczematization, secondary infection). The combination of primary and secondary lesion types produces a multifaceted clinical picture¹⁸.

Itching is invariably present and extends to areas adjacent to the lesion¹⁸. In the majority of patients itching is severe and is responsible for an important restriction of life quality¹⁹. Itching intensifies at night. **Excoriations** are the consequence of scratching. Scratching leads to haemorrhagic crusts forming on the top of **vesicles** and **secondary infection**. Superinfection is present in up to 40% of the patients¹⁸. If massive, the superinfection resembles pyoderma.

The characteristic **burrow** is the excavated tunnel in which the mite lives. It consists of a thin, curvy tract with a length of 1-10mm. A single clearly visible burrow is pathognomonic. However, in the tropics, burrows are only inconsistently present, and are difficult to see in pigmented skin^{18,20}. **Papules** are small and erythematous. They may be sparse or numerous and closely set. Over time papules may change into **vesicles**, and rarely into **bullae**.

Very young children often have widespread **eczematous erythema** or a **vesiculobullous rash**, particularly on the trunk, which is sometimes more symptomatic than the lesions themselves²¹. These lesions often extend over the

TABLE 7-2—Differential Diagnosis of Scabies

"Normal" scabies	Atopic eczema, contact dermatitis, lichen planus
Bullous scabies	Acropustulosis, bullous pemphigoid, pemphigus, arthropod bites, bullous impetigo, dystrophic bullous epidermolysis, drug reaction, cutaneous porphyria
Nodular scabies	Insect bites, urticaria pigmentosa, pseudolymphoma, Langerhans' cell histiocytosis, mastocytoma, prurigo simplex
Crusted scabies	Psoriasis, seborrhoeic dermatitis, Darier disease, ichthyosis, exfoliative dermatitis, chronic eczema

whole body, affecting skin folds, the palmoplantar region and the buttocks. The face and scalp can also be affected. Pruritus makes infants agitated. Very young babies do not scratch and may just look miserable or feed poorly²².

Elderly patients, especially those living in institutions, often have atypical scabies. They present with a **papular, vesicular and erythematous rash** disseminated over the trunk, limbs and even the back; burrows may be absent²³.

Crusted or disseminated scabies ("Norwegian scabies") is a hyperinfestation with myriads of mites present in **exfoliating scales** (up to thousands of mites per gram of scales). Typically, individual lesions confluent, so that the **hyperkeratosis** affects large areas. A variable degree of **erythema** is common. These patients are highly contagious. The condition occurs in individuals with a compromised immune responsiveness such as in AIDS, in HTLV-1 infection, after immunosuppressive therapies, in malignancies, and in patients with congenital immune defects. Cases have been reported in patients with leprosy and tuberculosis, endocrinopathies (diabetes mellitus and hypoparathyroidism), rheumatic conditions (systemic lupus erythematosus and dermatomyositis), or after treatment with corticosteroids²³. Children with neuropsychiatric disorders, or with Down's syndrome, are also prone to develop crusted scabies,

because they may be unable to eliminate mites through scratching.

Nodular scabies is a clinical variant in which extremely pruritic nodules are present on soft skin areas such as in the axillae, groins, on the buttocks, and genitals. It is a common presentation in infants. Nodules are firm, dull red or brownish masses that may persist for months and probably represent an intense hypersensitivity reaction to the mite or its products. Nodules do not contain mites. Superinfection and secondary eczematous changes due to intense scratching are common.

Bullous scabies is a distinct subtype that may arise in young children²⁴. Thinness of the stratum corneum and a loose adherence of the epithelial layers favour the appearance of bullae.

It is commonly assumed that mites penetrate and accumulate at certain predilection sites. However, a population-based study showed that lesions may develop at any area of the skin and that predilection sites vary between adult and pediatric patients¹⁸ (Table 7-3). Hence, the topographic site of a characteristic lesion is not sufficient to confirm a presumptive diagnosis. There are two exceptions: itchy papules on the scrotum and penis and itchy nipples associated with pruritic papular eruption in women are considered to be pathognomonic^{22,25}.

TABLE 7-3—Topographic Distribution of Lesions According to Age

Localization of lesions ^a	All (%)	Individuals infested <=7 years (%)	Individuals infested >7 years (%)	p-value
Abdomen	164 (83.7)	77 (82.8)	87 (84.5)	0.991
Inguinal area/medial parts of thighs	130 (66.3)	62 (66.7)	68 (66.0)	0.994
Axillas	122 (62.2)	67 (72.0)	55 (53.4)	0.238
Wrists	110 (56.1)	65 (69.9)	45 (43.7)	0.066
Interdigital spaces	105 (53.6)	60 (64.5)	45 (43.7)	0.138
Legs	100 (51.0)	56 (60.2)	44 (42.7)	0.205
Thorax	100 (51.0)	47 (50.5)	53 (51.5)	0.960
Back	99 (50.5)	51 (54.8)	48 (46.6)	0.592
Elbows	98 (50.0)	52 (55.9)	46 (44.7)	0.433
Buttocks	93 (47.4)	54 (58.1)	39 (37.7)	0.119
Arms	93 (47.4)	47 (50.5)	46 (44.7)	0.715
Hands ^b	66 (33.7)	42 (45.2)	24 (23.3)	0.033
Nipples/perimamillary area	58 (29.6)	21 (22.6)	37 (35.9)	0.173
Feet	45 (23.0)	34 (36.6)	11 (10.7)	0.001
Genitals	33 (16.8)	26 (28.0)	7 (6.8)	0.002
Scalp/neck/face	6 (3.1)	9 (9.7)	1 (1.0)	0.021
Total	196	93	103	

^a multiple observations possible

^b other parts than the interdigital spaces and the wrists

Case history/Family history/Travel history

Recent adoption may be a hint for the diagnosis of scabies in the mother²⁶. In children scabies occurred after regularly visits to an infested grandparent²⁷. Scabies in sexually active male adults may be associated with recent travel to developing countries²⁸.

Burrow Ink Test

The Burrow Ink consists of gently rubbing a suspect papule with the underside of a fountain pen, covering it with ink. The excess ink is then wiped off with alcohol-saturated gauze. If a burrow is present, the ink will track down it and outline the limits of the canal (Figure 7-3).

For several decades, the Burrow Ink Test was the diagnostic procedure most widely used in routine dermatology²⁹. However, its suitability is limited by several factors. First, burrows are inconstantly present and their occurrence varies between 7% and 92%²⁹. Second, burrows are often obliterated by scratching, formation of crusts, or superinfection. Third, in darkly pigmented skin neither a burrow is visible nor ink penetrating into it. Fourth, a visible burrow is not necessarily inhabited by a mite³⁰.

Studies on the diagnostic validity of the Burrow Ink Test are inconclusive. Sarwat et al.³¹ used this approach in Egyptian patients with scabies. Only 40% of the patients had visible burrows; in 85% of these patients the Burrow Ink Test was positive. Woodley and Saurat²⁹ compared sensitivity and specificity of the Burrow Ink Test with a superficial shave biopsy. The Burrow Ink Test had a specificity of 100%, but a sensitivity of only 24%.

Extraction of mites from burrows

Kenawi et al.³² removed mites from their burrows by the aid of a hand lens using a flat sharp needle and transferred the ectoparasite to a slide for microscopical analysis. The

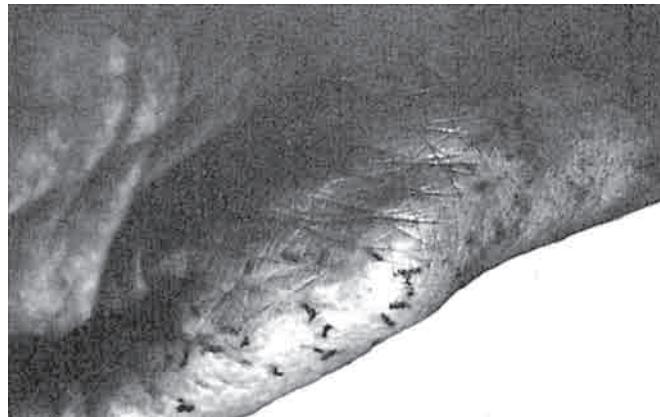


FIGURE 7-3 The thenar area with multiple burrows stained with ink
Source: Woodley and Saurat JAAD 1981: 4:715–722, reprinted with permission.

method has never been compared to other diagnostic approaches and has the same constraints as described for the Burrow Ink Test.

Skin scraping

Various types of skin scraping procedure exist. Usually a suspicious lesion is scraped with the edge of a scalpel blade or a sterile scarificator and the material obtained is transferred to a slide. A drop of 10-40% potassium hydroxide is added and the specimen is then examined at 100x magnification (Figure 7-4). Chlorasol Black E stains the cuticle of mites dark blue and allows to differentiate between fecal pellets (scybala) and artifacts³³ (Figure 7-5 A,B). A variation of the technique is to mix the scraping with a drop of glycerol or mineral oil³⁴. A drop of mineral oil can also be applied on the skin first and the scraping is performed afterwards. No comparisons with regard to diagnostic validity for the different modifications of skin scraping exist.

Palicka et al.³⁴ modified skin scraping in the way that first they wetted a suspicious lesion with a cotton swab dipped into 10% potassium hydroxide. The lesion was left to macerate for one minute in children and two minutes in adults. With the stump edge of a scalpel blade the lesion was scraped thoroughly. The specimen was transferred to a slide, mixed with a drop of water and examined at 100x magnification. The macerated area of the skin was neutralized with an acid ointment, such as unguentum acidi borici. Whether this modification performs better than the original method is not known.

Skin scraping has several constraints. First, the sensitivity seems to depend on the age of the patient, being considerably lower in adults than in children, as well as on gender³⁴. Second, it also depends on the topographic localization of the lesion and the clinical presentation (unscratched lesions are more valuable)¹⁷. Third, scrapings contain all developmental stages of the parasite. In a study in 151 patients Palicka et al.³⁴ observed adult mites



FIGURE 7-4 Sarcoptes mite identified in skin scraping (original magnification x200) Source: Neyhaber und Wolff, CMAJ, 2008;178:1540–1541, reprinted with permission.

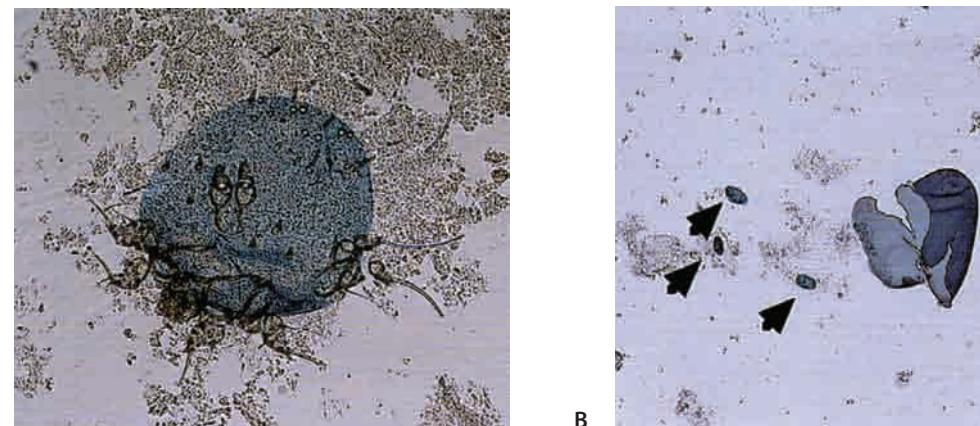


FIGURE 7-5 Staining of skin scraping with Chlorazol Black E. Adult female (A), eggshell fragments and scybala (B). Original magnification x100
Source: Uenotsuchi et al., *J Dermatol* 2004; 31:511–512, reprinted with permission.

in only 18% of the samples, larvae and juveniles in 9%, eggs in 68%. The remaining specimens contained egg shells and other parasite debris. Bhutto et al.³⁵ made similar observations. This is of importance, since only adult mites are easily identified and the identification of other developmental stages requires experience or a special staining (see above). Finally, even if several scrapings are performed and all are negative this does not exclude the presence of scabies¹⁷.

Bhutto et al.³⁵ embedded scraped material in non-fluorescent glycerin and examined the specimen with a fluorescence microscope. The authors claimed that eggs and egg shells were easily detectable by fluorescence microscopy, whereas they are difficult to visualize under a light microscope. In glycerol preserved specimens can be kept for at least six months, allowing re-examination of a slide by an expert. Siderits et al.³⁶ have prepared a commercially available kit containing the necessary material for several skin scrapings.

Taken together, skin scraping has an excellent specificity but only a low sensitivity for ordinary scabies, due to the low numbers of parasites. The sampler's experience also influences its sensitivity

Dermoscopy, epiluminescence microscopy, confocal microscopy

In 2004 Prins et al.³⁷ suggested the use of a handheld dermoscope with a 10x magnification for the in vivo detection of *S. scabiei*. The authors described a delta-glider-like triangle (synonym “delta wing jet sign”, “jet with contrail pattern”) which they considered to represent an adult mite. In fact, it had been shown previously that the dark triangle corresponds to the head of the mite and its front legs³⁸. These are brown in color, whereas the abdomen is milky transparent. In French the hang-glider-like triangle is called the “circumflex-accent-sign” (“^”)³⁹ (Figure 7-6).

Recently, Yoshizumi and Harada detected another pathognomonic pattern and called it the “wake sign”,

because of its reminiscence of the wake left on the surface of water by a moving bird⁴⁰. The “wake” indicates the direction of the burrow at the end of which the head of the mite is visible as a “^”.

In a prospective, evaluator-blinded study the diagnostic validity of dermoscopy was compared to the ex vivo microscopic examination of oriented skin scraping; i. e. scraping of an area where a mite had been identified/suspected by dermoscopy³⁹. The sensitivity of dermoscopy was 91% (95% confidence intervals 86-96%) and that of oriented skin scraping 90% (95% CI 85-96%). The specificity of dermoscopy clearly depended on the experience of the dermoscopist and was 73% for “beginners”, 81% for trained and 92% for experienced dermoscopists; sensitivity, though, did not depend on experience. Diagnostic accuracy also increased with experience. Patients in this study were mostly Caucasians, presumably with lightly pigmented skin.

Walter et al. (2010)⁴¹ also used a prospective, evaluator-blinded design in patients from a slum in Brazil to compare



FIGURE 7-6 “Delta-wing sign” identified b dermoscopy (original magnification x10). Source: Dupuy et al. *JAAD* 2007;56: 53–62, reprinted with permission.

the diagnostic validity of dermoscopy and of skin scraping performed without help by the dermoscopist. The majority of the patients had colored skin. The authors determined a sensitivity of 83% (95% CI 70-94%) for dermoscopy and of 46% (95% CI 30-62%) for skin scraping. The sensitivity of dermoscopy was higher in recent as compared to chronic infestations (88% versus 76%) and increased with the severity of scabies (light scabies 80%, moderate scabies 85%, severe scabies 93%). The authors were unable to identify the characteristic delta wing in patients with dark skin.

Dermoscopy may require extensive time to come to a conclusive diagnosis: Dupuy et al.³⁹ needed 10-20 minutes in 18%, 5-10 minutes in 33% and less than 5 minutes in 49% of the cases.

In videodermatoscopy a camera equipped with a special lens is applied to the skin which allows a magnification from 10x to 1000x. This technique allows examination of the skin to the level of the superficial papillary dermis. Micali et al. have introduced videodermatoscopy for the diagnosis of scabies in 2000⁴². Lacarruba et al. compared videodermatoscopy to skin scraping in small case series and noticed a similar sensitivity⁴³. However, the study design was not sufficiently robust to come to a definitive conclusion. A hand-held epiluminescent stereomicroscope with a magnification of 20x to 40x seems equally suitable⁴⁴ and can replace the expensive stationary instrument. Recently, Levitt⁴⁵ showed that in light skin a burrow can also be identified using a high-resolution digital camera equipped with a macro lens, when the photo is magnified by 150%.

Argenziano et al.³⁸ applied epilumiscence microscopy with a 40x magnification and considered it a valid diagnostic tool. Again, this study was not sufficiently robust to conclude on the diagnostic validity of the technique. Burrows and mites can also be visualized with reflectance-mode confocal microscopy⁴⁶.

Since videodermatoscopy and epiluminescence microscopy require considerable skills and investment, their application is restricted to well-resourced tertiary care centers. Whether these approaches can be successfully used in patients with dark skin remains to be demonstrated. They clearly are an alternative in children when it is difficult to perform skin scrapings.

Histopathology

Although, in scabies a biopsy is not indicated – except if a malignancy has to be ruled out as a differential diagnosis - in single cases the examination of multiple step sections might reveal diagnostic hints in patients in whom dermoscopy and skin scraping have failed. Kristjansson et al.⁴⁷ noticed pink, pigtail-like structures that connected to the stratum corneum. The authors provided evidence that the pigtail-like structures are egg fragments left behind after the mite had hatched. Usually, the histological appearance of a lesion is that of a nonspecific, delayed hypersensitivity reaction with superficial and

deep perivascular inflammatory mononuclear cell infiltrates containing eosinophils, as well as papillary edema and epidermal spongiosis⁴⁸.

Immunodiagnosis

A few studies have addressed B cell responses in patients with scabies. Roberts et al. (2005)⁴⁹, Arlian et al., (2004)⁵⁰, and recently Walton et al.⁵¹ observed extremely high levels of polyclonal IgE and IgG4 in patients with crusted scabies (with median IgE levels at 17 times the upper-limit of normal), but normal levels in patients with only few mites. Eosinophilia occurred in about 60% of the patients with crusted scabies⁵¹. Whether these patients were concomitantly infected with intestinal helminths was not reported by the authors.

It is known that patients sensitive to house dust mites, but with no history of scabies, have circulating IgE antibodies that recognize antigens in *S. scabiei* var. *canis* extract⁵². Furthermore, Western blot and radioallergosorbent assays demonstrated that individuals with scabies showed strong IgE binding to house dust mite extract⁵³. Since scabies mites and house dust mites are phylogenetically related arthropods, it is not surprising that they have homologous allergens¹⁷. Taskapan and Harmanyeri explored the cross-reactivity of mite allergens for the diagnosis of scabies⁵⁴. Eighty-eight % of their patients showed positive reactions in a skin prick test and 68% had a positive allergy patch test against house dust mite. Patients had no history of atopy. However, the study design did not allow to conclude on sensitivity and specificity of the reactions.

Enzyme-linked immunosorbent assays developed for the detection of antibodies to *S. scabiei* in pigs and dogs are commercially available. These assays rely on whole-mite antigen preparations derived from *S. scabiei* var. *suis* or the itch-mite of the red fox, *S. scabiei* var. *vulpes*¹⁷. A recent study looking at cross-reacting IgG antibodies to the fox mite antigen in human scabies reported a sensitivity of only 48%, in comparison with 80% in pig scabies and 84% in dog scabies⁵⁵. Purified, well-characterized recombinant scabies mite allergens with standardized protein contents could potentially be useful in the future¹⁷.

PCR is unlikely to become a reliable test for widespread use, due to the generally low mite burden and, thus, low sensitivity¹⁷.

Resource-poor setting

In endemic areas in the developing world scabies is usually diagnosed using a case definition. Obviously, the sensitivity and specificity of a case definition depends on the setting and tends to be overestimated. For instance, a case definition used in a population-based study in a scabies-endemic area in rural Brazil had a sensitivity of 65% and a specificity of only 43% (Feldmeier H. unpublished observation). In this study scabies was diagnosed,

if two out of three requirements were fulfilled: pruritus which intensified at night, presence of the lesions for >2 weeks, at least one more household member with similar lesions¹⁸.

In an observer-blinded, prospective study in an impoverished community Walter et al.⁴¹ used the adhesive tape test described by Katsumata and Katsumata³⁰. In this test an adhesive tape of the size of a glass slide is firmly pressed on a lesion, then pulled off rapidly, transferred to a slide and examined at x 10 to x 40 magnification. The adhesive tape test had a sensitivity of 68% (95% CI 52-81%) and a specificity of 100%. Its sensitivity was significantly better than that of skin scraping and it did neither depend on the duration of infestation nor on the severity of scabies.

In a setting with poor health infrastructure presumptive therapy with oral ivermectin (2x200µg/kg body weight) can be used as a substitute of clinical diagnosis. In patients with scabies itching disappears or decreases shortly after the first or the second dose of ivermectin.

TUNGIASIS (SAND FLEA DISEASE)

Parasite and life-cycle/Epidemiology

With a maximal length of 1 mm, *Tunga penetrans*, also called chigoe- or jigger-flea (Linneus 1758), is the smallest flea species. True to its species name, the female burrows into the skin of its host. There it remains for a period of up to 5 weeks, during which it matures, produces and releases eggs and finally dies. Within 1–2 weeks, the flea increases its volume by a factor of roughly 2,000, frequently reaching a diameter of up to 10 mm⁵⁶. The entire parasite remains completely buried in the epidermis, with the exception of the posterior parts of the abdomen bearing the anus, the genital opening and four pairs of large stigmata. The protruding rear end leaves a sore, 240–500 mm in diameter, which serves an entry point for pathogenic micro-organisms.

When eggs reach the ground larvae develop into adult fleas. Off-host development needs about 18 days and depends on soil temperature and humidity. Adult fleas can jump, but usually reach a human host by running on the surface of his skin.

Tungiasis is a zoonosis affecting a broad range of wild and domestic animals. Man is as appropriate as a host as other mammals. Sand flea disease occurs in most countries of South America, in the Caribbean and in sub-Saharan Africa. It is endemic in many resource-poor communities in urban centers, in the hinterland or the littoral.

Clinical findings

The infestation with *T. penetrans* is a dynamic process, and the aspects of the lesion changes with time. Eisele et al.⁵⁶ have described the natural history of tungiasis in man

and have classified the disease into five stages ("Fortaleza Classification"). In stage I the flea is in *statu penetrandi* (30 min to several hours), and a reddish spot of about 1 mm appears (Figure 7-7A). In stage II the hypertrophy of the flea's abdomen begins and the parasite becomes obvious as a growing whitish or mother-of-pearl-like nodule (one to two days after penetration) (Figure 7-7B). In the protruding rear cone of the flea, the anal-genital opening appears as a central black dot. The lesion is surrounded by an erythema. In stage III the hypertrophy is maximal. A round, watch glasslike patch appears which is frequently accompanied by hyperkeratosis and desquamation of the surrounding skin (Figure 7-7C). Expulsion of eggs and feces are typical in this stage (Figure 7-7C). The lesions are usually painful and produce the sensation of a foreign body expanding under the skin. In stage IV a black crust covers an involuted lesion with a dead parasite (three to five weeks after penetration) (Figure 7-7D). A residual "scar" in the *stratum corneum* is characteristic for stage V (six weeks to several months after penetration) (Figure 7-7E). The appearance of the lesion may be changed by superinfection and manipulation of the lesion by the patient or a carer.

Typically, *T. penetrans* affects the periungual area of the toes, the heels and the soles. However, embedded sand fleas can be found on almost every part of the body, such as the hands, elbows, neck, buttocks and the genital region⁵⁷. If several lesions exist simultaneously they are usually located in clusters. Such lesions show a honeycomb-like aspect. In the endemic area severe infestations with hundreds of embedded sand fleas are not rare.

In single cases lesions may take the aspect of a tumourous growth and in histological sections appear as pseudoepitheliomatous hyperplasia⁵⁸. Although tungiasis is a self-limited infestation, complications are common in the endemic area. Many patients report severe pain, and inflammation and fissures commonly hinders individuals from walking normally⁵⁹. Sequels include deformation and loss of toenails, as well as deformation of digits. Superinfected lesions lead to formation of pustules, suppuration and ulcers. *Staphylococcus aureus* and streptococci frequently occur, but other aerobic and anaerobic bacteria (including clostridia) are also found⁶⁰. In non-vaccinated individuals tungiasis may lead to tetanus⁵⁷.

The diagnosis of tungiasis is made clinically. Patients from an endemic area diagnose tungiasis correctly. In travelers even the untrained physician will recognize the ectoparasitose if he considers the natural history of the disease. The patient typically complains about local itching, pain and the sensation of a foreign body.

The observation of eggs being expelled or eggs attached to the skin around the rear cone and the release of brownish threads of faeces are pathognomonic signs. Faeces threads are of a helical structure and often spread into the dermal papillae (Figure 7-7F). Expulsion of eggs can be provoked by massaging the hypertrophy zone slightly.

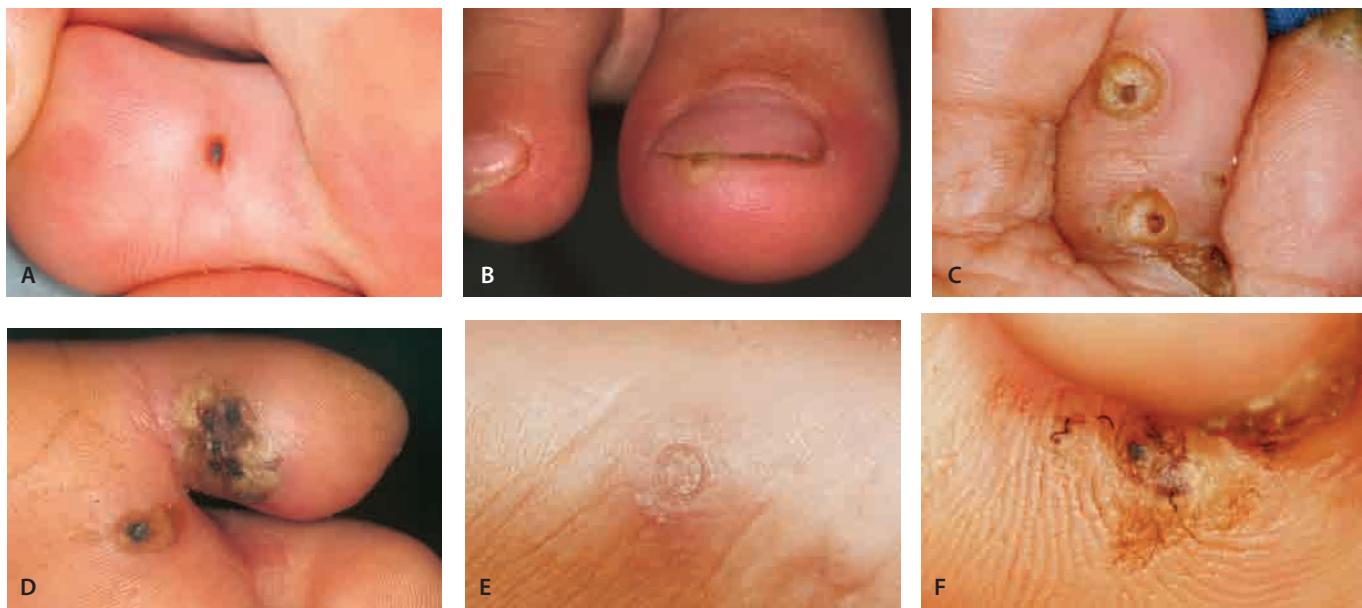


FIGURE 7-7 Recently penetrated sand flea. The black dot in the center of the lesion indicates the last abdominal segments of the parasite (A). Lesion in stage II at the rim of the nail. The circular yellow-whitish area is the hypertrophied abdomen of the embedded flea (B). Two lesions at the base of a toe. The distal lesion shows a wrinkled appearance, an indication that involution of the lesion has already begun (stage III). Next to the other lesion an egg is visible. A fissure has formed below the distal metatarsal joint (C). Cluster of lesions at the base of the fifth toe surrounded by pus. Lesions are covered by a black crust (stage IV) (D). Circular 'scar' at the rim of the foot. A sand flea was embedded here several weeks ago (E). A cluster of three lesions at the base of a toe. Two faecal threads are located left to the cluster. One faecal thread is being ejected. Faecal material is spread in dermal papillae (F).

Differential diagnoses include verrucae vulgaris, myiasis, pyogenic infection/abscess, foreign bodies, acute paronychia, cutaneous larva migrans, dermoid cysts, dracunculiasis, melanoma, deep mycosis and bites or stings of other injurious arthropods.

Case history/Travel history

Residence in an endemic area is a good hint. Travelers with tungiasis commonly report having walked in infested places such as beaches or areas with stray dogs and cats.

Histopathology

A biopsy of the lesion followed by a histopathological examination is not indicated. However, in atypical tungiasis, such as lesions with a pseudoepitheliomatous appearance, a biopsy is useful. Histological sectioning may demonstrate the presence of the ectoparasite or of chitinous fragments. A systematic study in 86 patients showed – mostly unspecific – histological alterations in the epidermis in 70% and in the dermis in 95% of the patients (Table 7-4)⁶¹.

Laboratory methods

Hematological investigations are not helpful.

CUTANEOUS LARVA MIGRANS

Parasite and life cycle/Epidemiology

Hookworm-related cutaneous larva migrans (CLM) is a parasitic skin disease caused by infestation of human skin with larvae of animal nematodes, such as *Ancylostoma braziliense*, *Ancylostoma caninum*, or *Uncinaria stenocephala*. These nematodes live in the intestine of dogs and cats. Eggs shed in feces hatch in the superficial layer of the soil within 1 day, and develop into infective third-stage larvae after about 1 week. In a warm and humid environment, they can survive and remain infective for several months. Larvae penetrate into the corneal layer of the epidermis when human skin comes into contact with soil contaminated by animal feces.

Infestation through contaminated fomites is rare. In Italy a small outbreak of hookworm-related cutaneous larva migrans was reported involving six individuals with lesions on the anterior part of thighs, arms, and chest, caused by contaminated dried flowers used for decoration purposes⁶².

Because humans are an incidental host, in whom the normal larval development is abrogated, CLM is self-limiting. However, the ectoparasitosis may persist for several months, and rarely for a year⁶³.

Hookworm-related cutaneous larva migrans is endemic in resource-poor communities in the developing world, particularly in Brazil, India, and the West Indies. The

TABLE 7-4—Histopathological Findings in Tungiasis Patients

Type	n	(%)
Epidermis (109 biopsies)		
No alteration	33	30.3
Abnormal histological texture	76	69.7
Hyperplasia	43	56.6 ^a
Parakeratosis	34	44.7 ^a
Hyperkeratosis	16	21.1 ^a
Spongiosis	7	9.2 ^a
Pseudoepitheliomatous hyperplasia	2	2.6 ^a
Indicators of inflammation and/or superinfection		
Inflammatory infiltrate ^b	26	34.2 ^a
Micro-abscess, pus	28	36.8 ^a
Dermis (57 biopsies)		
No alteration	3	5.0
Abnormal histological texture	57	95.0
Inflammatory infiltrate ^c	57	100 ^d
Vasodilation/neovascularisation	4	7.0 ^d

^a Of epidermal sections with abnormal findings

^b Frequency of cells within infiltrate in decreasing order: neutrophils, eosinophils, plasma cells, giant cells

^c Frequency of cells within infiltrate: lymphocytes (mainly plasma cells) > eosinophils > neutrophils > mast cells > histiocytes

^d Of dermal sections with abnormal findings

Source: Feldmeier et al. Parasitology Research 2004, 94:275–282.

infestation is frequent in areas where stray dogs and cats are common or where pets are not treated regularly with anti-helmintics. The disease occurs sporadically or in the form of small epidemics in children in high-income countries

and is an important disease in tourists who have visited tropical beaches. There is a distinct seasonal variation of hookworm-related cutaneous larva migrans, with a peak incidence during the rainy season.

General remarks

For decades, the terms cutaneous larva migrans and creeping eruption have been used as synonyms. The first term describes a syndrome and the second a clinical sign, present in a variety of conditions. A creeping eruption is defined clinically as a linear or serpiginous, slightly elevated, erythematous track that moves forward in an irregular pattern (Figure 7-8A). It can be caused by animal hookworm and other nematode larvae (e.g. larva currens by *Strongyloides stercoralis*), or by parasites such as *Gnathostoma* spp and *Loa loa*, and larvae of parasitic flies (migratory myiasis).

Clinical findings

Usually, itching begins shortly after larvae have started to penetrate into the epidermis. A reddish papule appears at the penetration site in immunologically naive individuals and also in individuals sensitized previously. In most cases, 1–5 days after penetration the elevated track appears. However, studies on travelers have shown that the incubation period may last a month or even longer⁶⁴. The itching is intense and described as very uncomfortable by patients. A recent study demonstrated that 81% of patients with hookworm-related cutaneous larva migrans were prevented from normal sleep because of the intensity of itching⁶⁵. Pain indicates the presence of superinfection.

A study in an endemic area in Brazil showed that CLM is considered an important restriction of life quality⁶⁶. Lesions tend to become superinfected with pathogenic



FIGURE 7-8 Hookworm-related CLM on the hand. Two tracks with two excoriations are located closely to each other (A). Two larva migrans-associated bullae at the sole (B).



bacteria as a result of scratching. In resource-poor communities in Brazil, superinfection of lesions was observed in 8–24% of patients⁶⁵. Vesiculobullous lesions (Figure 7-8 B) occur in 9–15% of cases, with bullae sometimes reaching an impressive size of several centimeters⁶³. Very rarely, animal hookworm larvae may invade the viscera and cause pulmonary eosinophilia (Loeffler's syndrome).

Patients in endemic areas usually have multiple tracks. Up to 45 tracks have been observed in individuals living in slums⁶⁶. Travelers returning from an endemic area commonly present only a single or a few tracks.

The topographic distribution varies according to age. Small children show lesions on the buttocks, genitals, hands, and feet, whereas in older patients, the majority of lesions are located on the feet and buttocks⁶⁵ (Table 7-5). In tourists, typically the feet, buttocks, and thighs – body areas that typically come into contact with contaminated sand while walking or sitting on the beach – are affected.

In a population-based study Jackson et al.⁶⁵ noticed that on the average a larva migrated 2.7 mm per day. The length of the track is therefore a proxy of the duration of the infestation and helps to identify the place where exposure had happened.

The diagnosis of hookworm-related cutaneous larva migrans is easily made clinically and is supported by a travel history, or in an endemic setting, by possibility of exposure.

CLM may mimic scabies, loiasis, myiasis, cercarial dermatitis (the early phase of schistosomiasis), tinea corporis, and contact dermatitis. Considering the characteristic features of CLM, these conditions are ruled out

TABLE 7-5—Localization of Larval Tracks According to Setting

	Rural community ^a %	Urban slum ^b %
Feet	73	0
Legs	3	23
Buttocks	15	5
Genitals and/or inguinal area	8	5
Hands	1	7
Arms	0	11
Trunk	0	0
Head	0	9

^aJackson et al., 2006⁶⁵

^bHeukelbach et al., 2003⁶⁹

easily. CLM can mimic herpes zoster; however, the latter follows the anatomic path of a peripheral nerve and does not progress in the manner that the creeping eruption in CLM does. A serpiginous ganglion cyst has also to be considered as a differential diagnosis. Another condition of non-parasitic origin resembling creeping eruption has been a hair growing horizontally in the skin.

Videodermatoscopy

Micali and Lacarruba⁶⁷ have suggested videodermatoscopy as a tool to diagnose CLM. However, as even a single

What We Know

Pediculosis capitis

- The most sensitive method to diagnose active pediculosis capitis is wet combing. Visual inspection is the method of choice to identify a historical infestation. In resource-poor settings self-diagnosis by the patient or his carer is reliable.

Scabies

- The numerous modification of skin scraping and of the Burrow Ink Test indicate that none of the approaches are actually efficient. The sensitivity of both methods depends on a number of variables and usually is disappointingly low.
- Dermoscopy, videodermatoscopy, epiluminescence microscopy, and confocal microscopy are able to visualize adult mites (dermoscopy) or all developmental stages (videodermatoscopy, confocal microscopy) in patients with white skin. Specificity of these imaging techniques largely depends on the experience of the examiner.
- A presumptive diagnosis can be made on the basis of a local intense pruritus, pruritus that is worse at night,

the topographic localization of the suspicious lesion, and a history of contact with an other scabies case.

- Except in disseminated “Norwegian scabies” immunological investigations are not helpful.
- In resource-poor settings a locally validated case definition is a practical alternative. A presumptive therapy with oral ivermectin (2x200µg/kg body weight) can be used as a substitute of clinical diagnosis.

Tungiasis

- Tungiasis is diagnosed clinically taking into consideration the dynamic changes of embedded sand fleas and the natural history of sand flea disease.

Cutaneous larva migrans

- The diagnosis of cutaneous larva migrans is based on the clinical characteristics of hookworm-related creeping eruption together with a history of exposure. Histopathology is not helpful. A presumptive treatment with oral ivermectin is a practical alternative, since the pruritus disappears within 48 hours.

creeping eruption is diagnostic, there is no reason to use expensive instrumentation.

Histopathology

The invasive procedure only rarely identifies the parasites. Since the anterior end of the track does not necessarily indicate the place where the larva is located, it is difficult to perform the biopsy at the right place.

Laboratory investigations

Eosinophilia may or may not be present and is not specific. In a study on returning travelers only eight (20%) of 40 patients with CLM presented with eosinophilia, but infection status regarding other helminths was not known⁶⁸. However, a high eosinophil count can indicate migration of helminth larvae into the viscera, a rare complication.

Medical history/Travel history

A recent travel history to an endemic area, particularly in the rainy season, is a good hint for a presumptive diagnosis.

Resource-poor setting

In endemic area patients usually correctly identify their disease and paramedicals are experts, even if lesions are altered by intense scratching and superinfection. After a presumptive treatment with oral ivermectin (200µg/kg bodyweight) itching disappears or significantly decreases within 48 hours, and the lesion involutes within a couple of days.

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Diagnosis of Hirsutism

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INTRODUCTION

Hirsutism is defined as the presence of terminal (coarse) hairs in a male-like pattern of distribution in women and affects approximately 5-15% of premenopausal women worldwide.¹⁻⁴ Androgens are the strongest determinant for the transformation of fine vellus hairs to coarse terminal hairs in androgen-sensitive areas. Testosterone is the main circulating androgen and is produced in women by both the ovaries and the adrenals. The ovaries and adrenals produce 40-50% of the testosterone with the remaining 50-60% being produced by conversion of precursors, such as androstenedione in peripheral sites such as the liver and adipose tissue. Hirsutism must be distinguished from hypertrichosis, which is generalized excessive vellus hair

growth, that is primarily influenced by heredity or exogenous medications, such as glucocorticoids, but can be exacerbated by androgen excess.⁵

HORMONAL PATHWAYS

In women, the ovaries and adrenal glands are the source of androgens (Figure 8-1). The ovaries secrete androstenedione, testosterone, and dehydroepiandrosterone (DHEA). The adrenals primarily secrete DHEA and dehydroepiandrosterone sulfate (DHEAS), but also produce androstenedione and testosterone.⁶ Androstenedione, from the ovaries and adrenals, can either be converted to estrogen in granulosa cells or to testosterone in theca cells.⁷⁻⁸ Testosterone circulates in a free bioactive form and an

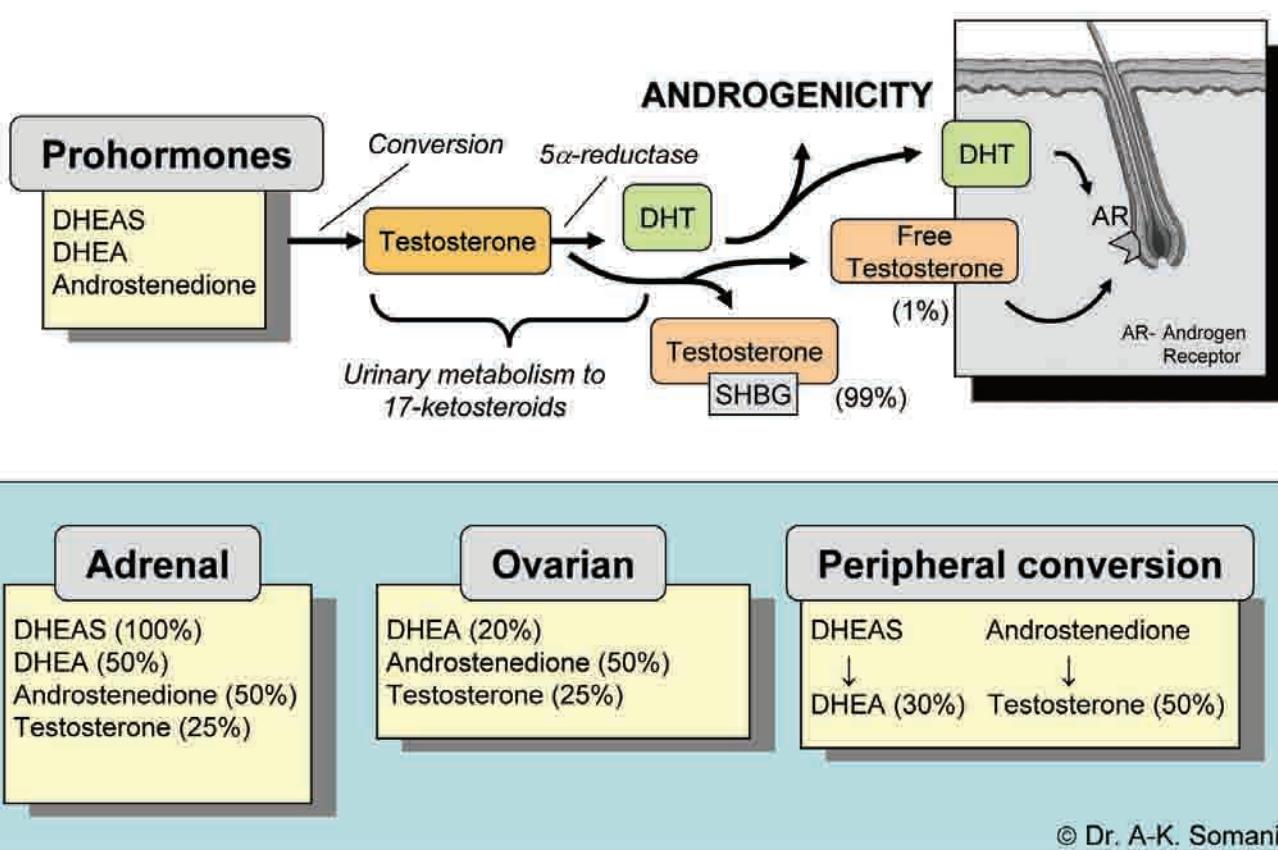


FIGURE 8-1 Sources of Androgens in Women. DHEA: dehydroepiandrosterone; DHEA-S: dehydroepiandrosterone sulfate; DHT: dihydrotestosterone; SHBG: sex hormone binding globulin.

inactive form bound to sex hormone-binding globulin (SHBG). Consequently, reduced levels of SHBG can lead to hyperandrogenism due to elevated levels of free testosterone. While estrogens increase the hepatic synthesis of SHBG, androgens, some synthetic progestins and glucocorticoids reduce SHBG synthesis. Excess insulin also decreases levels of SHBG.⁹⁻¹⁰

In the skin, testosterone can be converted to dihydrotestosterone (DHT), a potent stimulant for hair growth in androgen-sensitive areas, by the enzyme 5-alpha reductase. DHT acts directly on hair follicles producing terminal hairs where small, straight, nonpigmented vellus hairs once were. Weaker androgens, such as androstenedione and DHEA are also converted to testosterone and DHT in the skin to produce hair growth. The rate and amount of androgen secreted along with the rate of conversion in the periphery and the sensitivity of the androgen receptors on hair follicles are all factors in the development of hirsutism.¹¹⁻¹³ Both the androgen receptor activity and the 5-alpha reductase activity levels are influenced by genetics and may be heritable.¹⁴

Some areas of hair growth are independent of androgen effects (eyelashes, eyebrows, lateral, and occipital aspects of scalp), while other areas are very sensitive and respond with conversion to terminal hairs even at low levels of androgens (lower pubic triangle and axillary region). However, other areas such as the chest, lower abdomen, lower back, thighs,

arms, chin, face, and upper pubic triangle, only respond to high levels of androgens. Terminal hair growth in these areas defines hirsutism in women. Interestingly, androgens have a miniaturizing effect on terminal hairs over the vertex and crown of the scalp leading to androgenetic or patterned alopecia.¹³

Several studies have documented the psychosocial impact of hirsutism. Hirsutism is significant not only because of the social stigma it can carry leading to depression, social phobia, or body dysmorphic disorders,¹⁵⁻¹⁷ but also because it is often a visible sign of an underlying endocrine abnormality. Identification of the abnormality is important, as it is typically associated with increased risks for other disease processes, which may benefit from treatment (Figure 8-2). Eighty to 90% of patients with hirsutism will have measurable hyperandrogenemia, making it a powerful clinical marker for a potential underlying androgen excess disorder.¹⁸

Polycystic ovary syndrome (PCOS) is by far the most common underlying cause of hirsutism, accounting for 70-80% of hirsute women.¹⁹⁻²² Additional less common causes of hirsutism include hyperandrogenism, insulin resistance, Acanthosis nigricans (HAIRAN) syndrome accounting for 3%,¹⁸ 21-hydroxylase (21-OH) deficient nonclassic adrenal hyperplasia (NCAH), accounting for approximately 2%,²³⁻²⁴ androgen secreting tumors (approx. 0.2%), hyperprolactinemia, acromegaly, and thyroid dysfunction.

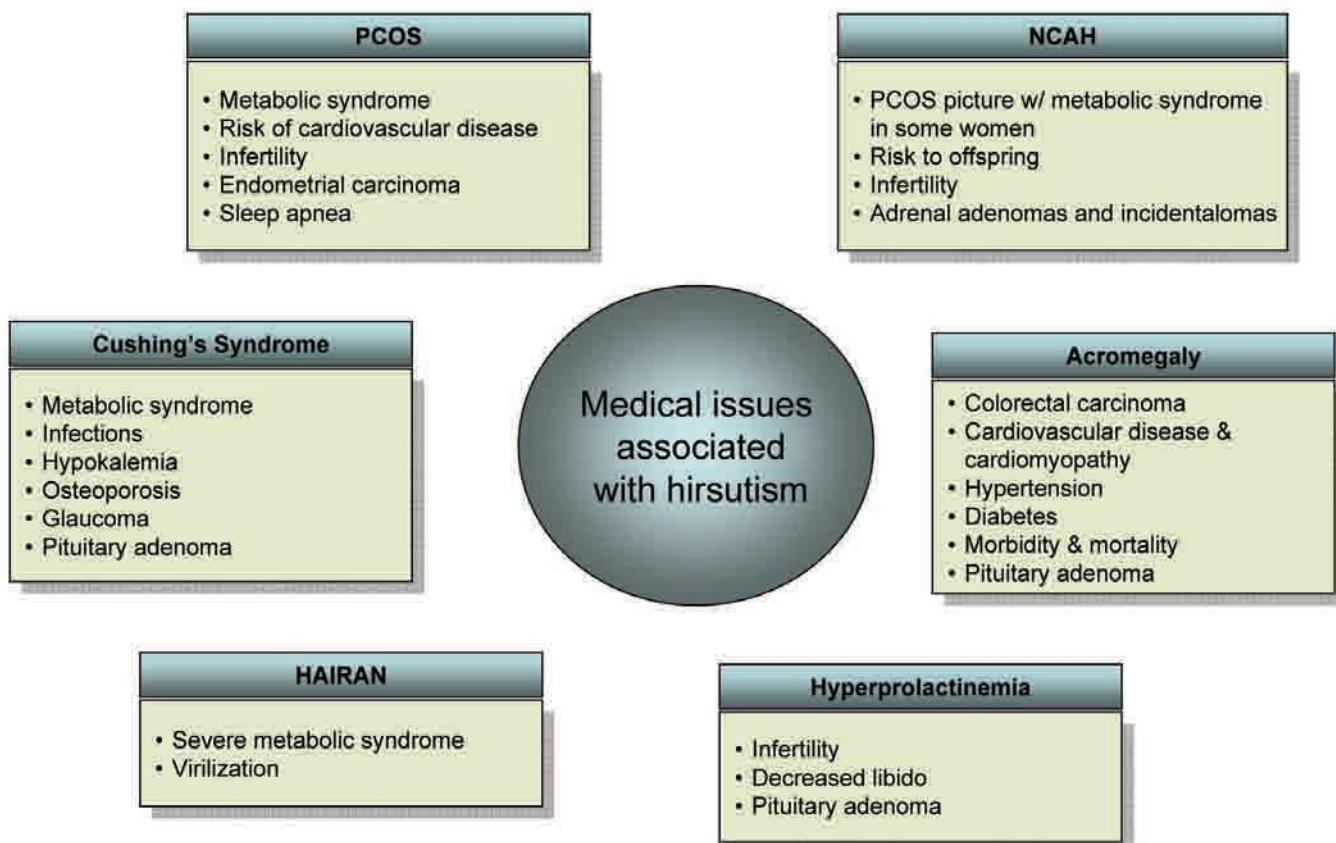


FIGURE 8-2 Medical issues associated with hirsutism

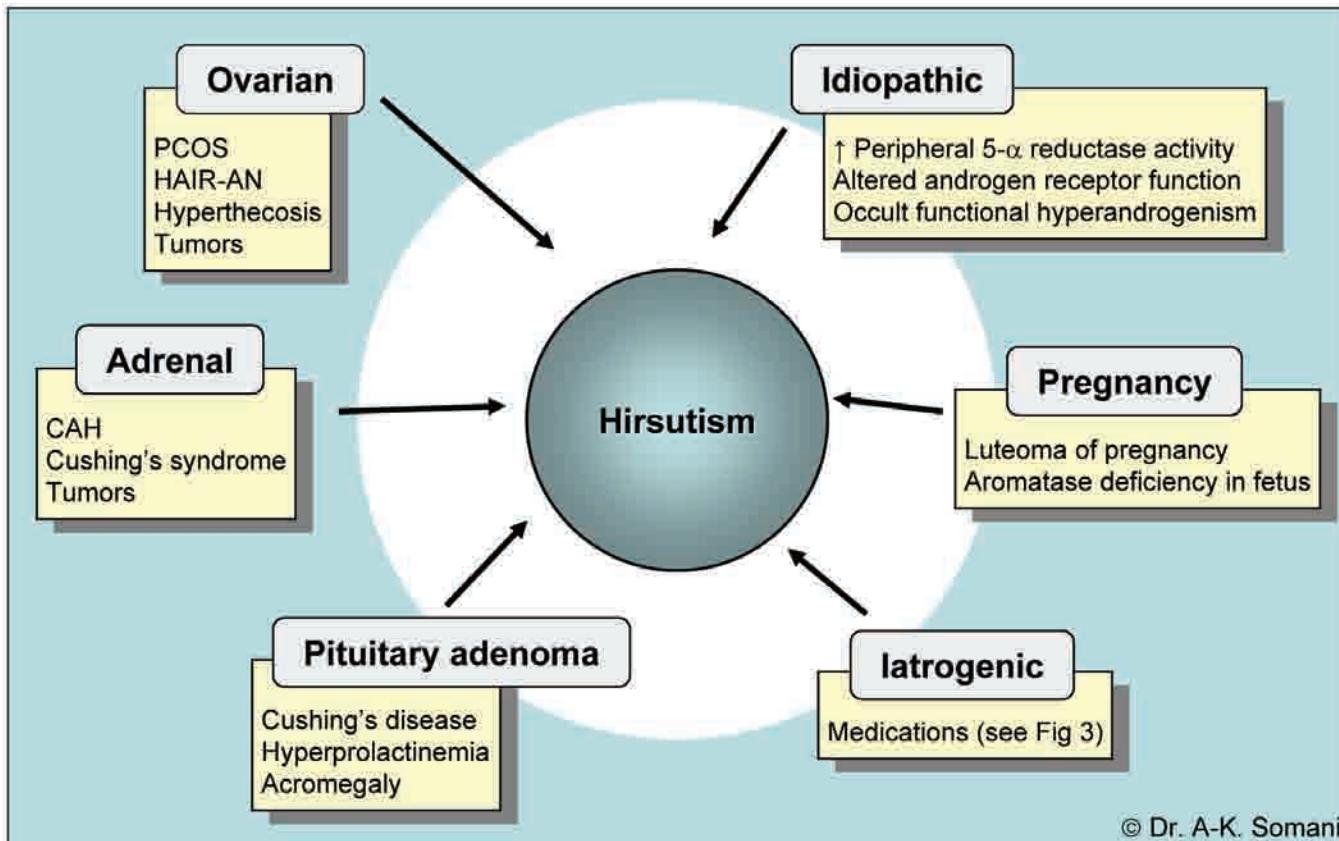


FIGURE 8-3 Etiologies of Hirsutism. PCOS: Polycystic ovary syndrome; HAIRAN syndrome: hyperandrogenism, insulin resistance, acanthosis nigricans; CAH: congenital adrenal hyperplasia.

(Figure 8-3). Five to 15% of hirsute women have “idiopathic” hirsutism. By definition, these women have regular menstrual cycles and no detectable androgen excess by conventional testing methods.^{12,18,25} Excess androgens can also be from exogenous sources such as androgen containing creams, danazol for endometriosis, oral contraceptives with an androgenic progestin, anabolic steroids and other medications (Figure 8-4).^{13,18,26–28}

Ovarian Causes

Polycystic ovary syndrome is estimated to affect 6.5–8% of reproductive age women worldwide and is inherited in an autosomal dominant pattern. Male relatives are carriers and may present with balding before age 30 and possible insulin-resistance.^{4,29–32} According to the 2008 Androgen Excess Society Guidelines, PCOS is defined by hyperandrogenism (clinically or biochemically) in association with ovarian dysfunction (oligo-anovulation and/or polycystic ovaries) with the exclusion of related disorders.³³ A proper diagnosis of PCOS is important, because it is associated with an increased risk for infertility, dysfunctional uterine bleeding, metabolic syndrome (i.e., type II diabetes, hypertension, hyperlipidemia, and increased BMI) and possibly cardiovascular disease.³⁴ Other studies have linked PCOS with obstructive sleep apnea, depression, nonalcoholic fatty liver disease and certain cancers such as endometrial

carcinoma.^{35–38} Hyperandrogenemia in PCOS is predominately caused by gonadotropin-dependent functional ovarian hyperandrogenism and to a lesser degree adrenal hyperplasia.^{39–40} As noted above, elevated androgen and insulin levels are associated with decreased levels of SHBG synthesis leading to elevated free testosterone in patients with PCOS.^{9–10} Insulin also directly affects ovarian androgen production.

HAIRAN syndrome is described as an extreme variant of PCOS with higher insulin levels and insulin resistance. HAIRAN syndrome actually represents a series of inherited syndromes, in which insulin receptor or post receptor defects lead to insulin resistance and a compensatory rise in circulating insulin. In addition to reducing SHBG levels, the excess insulin along with increased pituitary secretion of luteinizing hormone (LH), stimulates ovarian androgen secretion leading to hyperandrogenemia and virilization, that may mimic an androgen tumor.²⁷ Acanthosis nigricans results from the mitogenic effect of insulin on basal cells of the epidermis.^{41–42} Although there is clinical overlap with PCOS, women with HAIRAN syndrome are likely to have a greater degree of associated morbidity.

Ovarian hyperthecosis is caused by hyperplastic ovarian theca cells that have differentiated into luteinized stromal cells and actively produce androgens. These women are typically postmenopausal and have a long history of hirsutism in conjunction with signs of virilization. Their

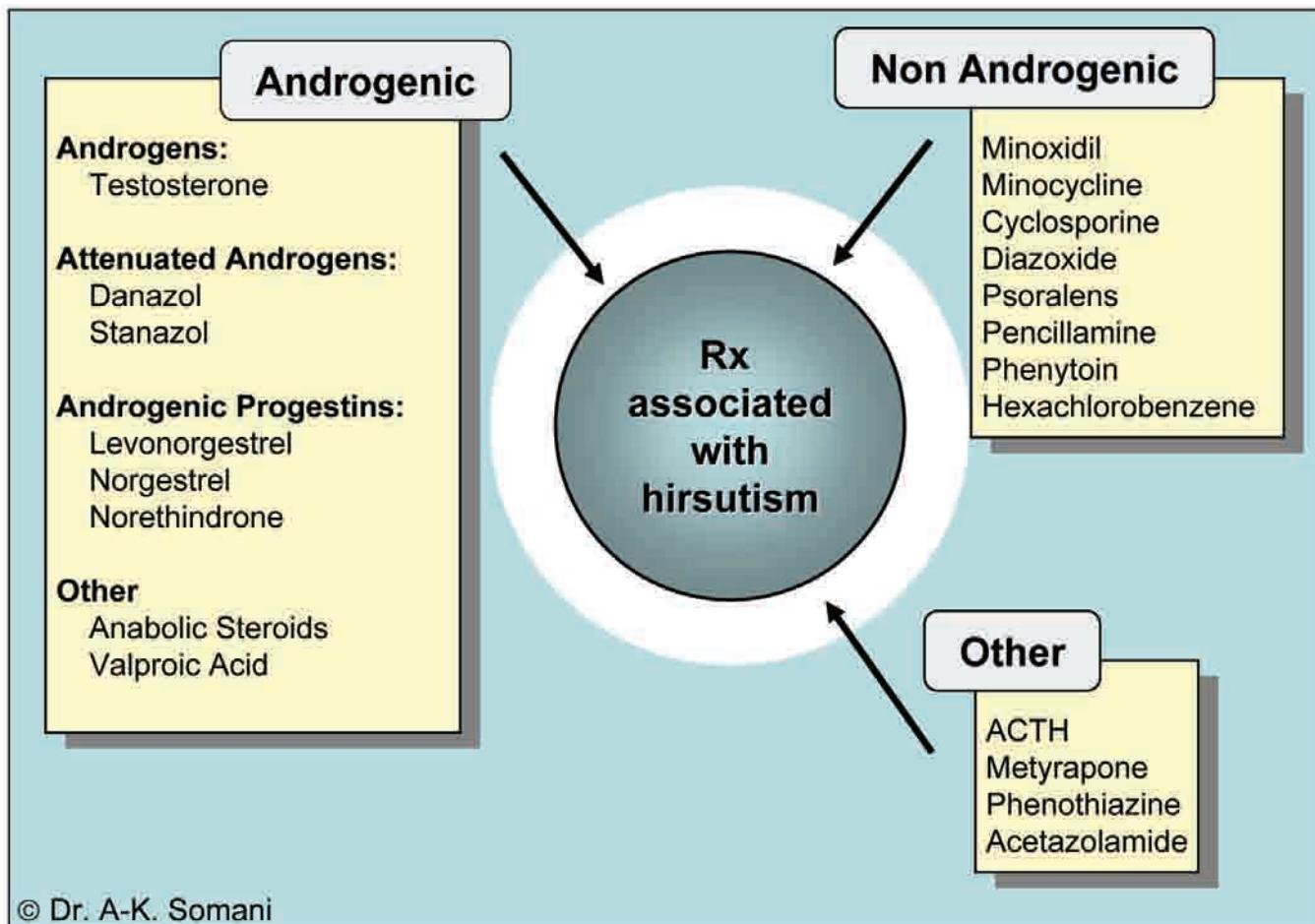


FIGURE 8-4 Medications associated with Hirsutism

clinical presentation may mimic that of androgen-secreting tumors. Like PCOS and HAIRAN, these patients are likely to develop insulin resistance.⁴³⁻⁴⁴

Adrenal Causes

Nonclassic adrenal hyperplasia is autosomal recessively inherited and is most commonly caused by a partial defect in the 21-hydroxylase enzyme (less commonly by defects in 11-hydroxylase or 3-β hydroxyl- Δ^5 -steroid dehydrogenase). It presents with a clinical picture similar to PCOS.^{18,45-46} The worldwide prevalence is approximately 2%; however, reports vary from 0.6-8.4% depending on the ethnicity of the population studied.²³ Patients commonly present with hirsutism in the prepubertal years, premature pubarche, menstrual irregularities, and virilization.⁴⁷⁻⁴⁸ The defective 21-hydroxylase enzyme results in accumulation of steroid precursors, including 17-hydroxyprogesterone (17-HP) and androstenedione. A decrease in cortisol production leads to an increase in ACTH, which stimulates the adrenals to produce steroids resulting in the accumulation of additional precursor steroids. Although typically a rare cause of hirsutism, it should be suspected in certain ethnic populations in which it occurs more frequently (see below).^{18,46}

Cushing syndrome is the result of adrenocortical hyperfunction leading to excess adrenal androgen and cortisol production and secretion. Cushing syndrome presents with signs and symptoms associated with corticosteroid excess, such as fat redistribution (central obesity, moon facies, dorsocervical fat pad), thinning of skin with striae, glucose intolerance, osteoporosis and proximal muscle weakness, in combination with signs and symptoms of hyperandrogenism and menstrual irregularities.²⁷

Hyperprolactinemia can affect the adrenal glands because they have a rich supply of prolactin receptors. Stimulation of these receptors can lead to increased synthesis of androgens.⁴⁹ However, the increased prolactin levels can also have an inhibitory effect on the conversion of testosterone to DHT. As a result, hyperprolactinemia rarely causes hirsutism, with an estimated prevalence of only 0.3%.^{18,50}

Additional Causes

Androgenic tumors of the ovary or adrenal gland are rare and are typically associated with androgen levels two times or greater the upper limit of normal along with a rapid onset of hirsutism and virilization. Signs and symptoms of virilization include a deepened voice, clitoromegaly,

increased muscle mass, and increased libido. When these are noted in association with Cushingoid features, adrenal tumors should be suspected, warranting imaging studies for confirmation.^{27,51}

Five to 15% of hirsute women have no evidence of biochemical androgenic excess or irregular menses and are defined as having “idiopathic” hirsutism.^{25,52} It has been demonstrated that as many as 40% of hirsute women reporting regular menstrual cycles, were actually found to be oligo-ovulatory when thoroughly evaluated with basal body temperature charting and luteal phase progesterone levels. These patients likely suffer from PCOS without overt menstrual irregularities.⁵² Some women with “idiopathic” hirsutism have a normal level of androgens, but have increased androgenic receptor sensitivity or increased local levels of 5 α -reductase resulting in relative peripheral hyperandrogenism at the hair follicle.⁵²⁻⁵³ Occult hyperandrogenemia can be uncovered in a large number of these women by gonadotropin-releasing hormone (GnRH) and corticotropin (ACTH) stimulation tests.⁵⁴ These are advanced tests that are currently available only on an experimental basis.

Some of the endocrine disorders underlying hirsutism may be inherited (e.g. PCOS, NCAH). Genetics can also influence the expression of hirsutism. For example, up to 30% of women with PCOS are not hirsute despite having elevated serum androgen levels comparable to their hirsute counterparts. This may be due to differences in peripheral androgen metabolism and in particular to variations in the 5 α -reductase type 1 and type 2 genes.⁵⁵⁻⁵⁶ Future development of genetic tests may be helpful in this regard.

CLINICAL EVALUATION

The goal of evaluating hirsutism is to identify the underlying etiology. The first step involves identifying and quantifying the degree of hirsutism as a baseline using one of the described visual scoring methods. The degree of hirsutism does not always correlate with the degree of hyperandrogenemia,¹⁸ but is often used to determine the extent of evaluation warranted.^{39,57} A thorough assessment of methods used to camouflage or remove hair is essential to accurately appreciate the degree of hirsutism. Many women with seemingly “mild” hirsutism use various methods to camouflage or remove unwanted hair, especially in more visible areas, and this may impact the examiner’s assessment if this information is not accurately obtained from the patient.¹² In addition, a focused history and appropriate physical examination are essential for guiding more extensive investigations to identify rare underlying etiologies or associated comorbidities. Tables 8-1 and 8-2 describe the key features of a focused history and physical examination for evaluating hirsute women. Current and prior medications should be assessed for those potentially linked to hirsutism (Figure 8-4), and assessment for associated medical problems, family history and psychosocial impact should be ascertained.

TABLE 8-1—Key Points for History Assessment

Clinical Data	History
History of present illness	Onset and progression of hirsutism—key determinant for further evaluation Sites & extent of hirsutism Psychosocial impact Treatments to date Use of skin irritants Change in body habitus
Associations	Alopecia Acne Seborrhea
Menstrual history	Age of onset Regularity Dysfunctional uterine bleeding
Reproductive history	Infertility
Past Medical History	Diabetes Hypertension Cardiovascular disease
Family History	Hirsutism Male relatives with excess hair or diabetes Male patterned alopecia prior to age 30
Medications	Use of medications associated with hirsutism (see Table 8-3) Use of oral contraceptive pills
PCOS	Weight gain, polydipsia, polyuria due to glucose intolerance, hypertension, hyperlipidemia, sleep apnea
HAIR-AN	Weight gain, polydipsia, polyuria due to glucose intolerance, hypertension, hyperlipidemia +/- virilization
Insulin resistance syndromes	Polydipsia, polyuria
NCAH	Ethnicity, amenorrhea, irregular menstrual cycles, premature pubarche, infertility +/- polydipsia, polyuria
Thyroid dysfunction	Hot or cold intolerance, weight changes, tremors
Cushing syndrome	Weight gain, striae, increased infections, easy bruising, fragile skin, weakness with rising from sitting position or when combing hair, insomnia
Hyperprolactinemia	Galactorrhea, infertility, oligo or amenorrhea, decreased libido
Pituitary Tumor	Visual disturbance, headache
Tumors- Adrenal/Ovarian	Virilization-increased libido, muscle mass, deepened voice, and clitoromegaly

TABLE 8-2—Focused Physical Examination

Clinical Data	Physical examination
Vital Signs	Height, weight and BMI Blood Pressure
Quantification of hirsutism	mFG score
Skin	SAHA: acne, seborrhea, hirsutism, patterned alopecia
PCOS	Acanthosis nigricans, SAHA, obese or lean
HAIR-AN	Acanthosis nigricans +/- signs of virilization-increased muscle mass, deepened voice and clitoromegaly
NCAH	High risk ethnicity, ±PCOS phenotype
Thyroid dysfunction	Weight change, dull facies, malar rash, generalized myxedema, tremors, exophthalmos, pretibial myxedema
Cushing's syndrome	"Fat redistribution"*, ecchymosis, proximal muscle weakness
Hyperprolactinemia	Galactorrhea
Acromegaly	Frontal bossing, prognathism, enlarged face, hands and feet, macroglossia, excessive sweating, pigmented skin tags and acanthosis nigricans
Pituitary Tumor	Visual field defects
Tumors-Adrenal/Ovarian	Palpable ovarian/abdominal mass, Virilization – increased muscle mass, deepened voice and clitoromegaly.

*Fat redistribution with increased abdominal girth, moon facies, dorsocervical fat pad, and slim limbs. PCOS: Polycystic ovary syndrome; HAIRAN syndrome: hyperandrogenism, insulin resistance, acanthosis nigricans; NCAH: nonclassic adrenal hyperplasia.

SEARCH METHODOLOGY

A search of Medline was conducted on the Ovid database using the key word "hirsutism" and "diagnosis" including all its specific terms. Searches were limited to studies in humans and articles published in English. References were evaluated along with additional references found in the original documents reviewed. Evidence presented in this chapter is derived from primary evidence, consensus reports of expert committees and clinical practice guideline publications. Most of the primary evidence is based on retrospective and prospective studies. Randomized controlled trials and meta-analyses were not available in the literature.

RESEARCH QUESTIONS AND ANSWERS

1. Which of the described visual scoring systems for hirsutism is most widely accepted for clinical use?

The clinical diagnosis of hirsutism is most commonly made using the Ferriman-Gallwey (FG) scale or a modification

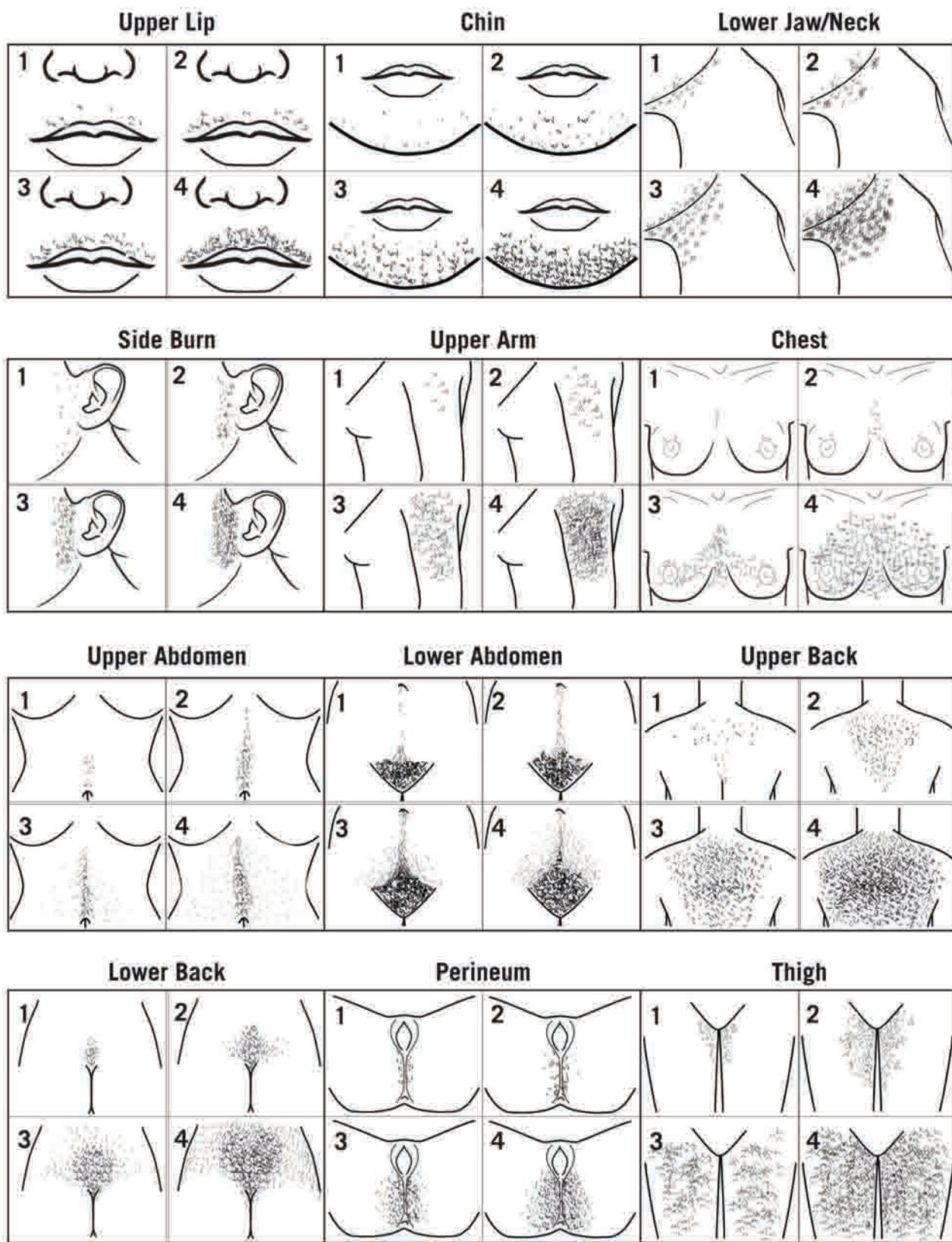
of it (Figure 8-5). The FG scale is a semi-quantitative visual scoring system originally described in 1961 based on a study of 430 consecutive women attending a general medical clinic in the United Kingdom of predominately-white race, ages 15-74 years. The system subjectively evaluated hair growth in 11 different areas (upper lip, chin, chest, upper back, lower back, upper abdomen, lower abdomen, arm, forearm, thigh and lower leg) and assigned each area a score from 0-4 based on the amount of hair present. A score of 0 is defined as the absence of terminal hairs and a score of 4 is defined as extensive terminal hair growth. It was noted that the forearm and lower leg were less sensitive to androgens and not further included, giving a maximum possible score of 36. It was determined that 4.3% of the subjects had a score greater than seven, which was consistent with the expected prevalence of hirsutism. Therefore, a score of 8 or greater was defined as hirsutism, with a score of 8-15 being defined as mild and >15 as moderate to severe hirsutism.¹

The Ferriman-Gallwey scale was later demonstrated in a study of 88 hirsute women to validly reflect androgen excess, but not directly correlate to more objective measures such as microscopic measurements of hair shaft diameter and counting of individual hair shafts when evaluating the forearm, abdominal wall and thigh.⁵⁸ Other more objective methods described in the literature include weighing hairs obtained by dry shaving or determining the density of hairs by direct counting or photography.⁵⁹⁻⁶⁰ These methods are more expensive, more complex and have poor patient acceptance, making them poorly suitable for routine clinical use.

In 2000, Knochenhauer et al. conducted a study to evaluate the utility of a significantly simplified modified FG (mFG) scale using only the chin and abdomen to correctly identify hirsutism.⁶¹ A total of 695 hyperandrogenic women were evaluated with both the standard mFG scale and with the simplified index.⁶² Based on an mFG score of ≥8, 50.1% of the participants were determined to have hirsutism. The specificity and sensitivity of evaluating only the chin and lower abdomen was then compared to the mFG results. A total of 84% and 91% of hirsute women had chin or abdomen hair scores respectively that were ≥2. Using a score of greater than or equal to two in the two areas had a sensitivity of 100%, but a specificity of only 27%. The PPV will vary depending on the population prevalence and if the general population prevalence is estimated at 5%, the simplified index would give a PPV of only 1%, making this method essentially useless in low prevalence populations.⁶¹

The Practice Committee of the American Society for Reproductive Medicine recommended a modification of the FG scale that includes the sideburns, lower jaw and upper neck, and the perineum in addition to the original nine areas described, giving a maximum score of 48 (Figure 8-5).²⁷ The European Consensus Guidelines acknowledge the limitations of the FG scale due to its subjective nature, but they too recommend the use

Modified Ferriman-Gallwey Scale



of a modification of the original FG scale.⁵⁷ A recent systematic review of the literature on scoring hirsutism concluded that the mFG scale has been more widely used in peer-reviewed articles than other assessment tools and continues to be a clinically useful instrument for visually assessing hirsute women.⁶³

2. What are the limitations of the FG scale?

The Ferriman-Gallwey scale either in its original form or in modified versions remains the current standard for grading hirsutism. However, it has significant limitations due to its subjective nature. Intra-observer variability has been shown to be within 3 points, but in a study of 21 hirsute patients, the inter-observer variation was found to be as much as 60% higher or 46% lower between observers.⁶⁴ The scale criticized for assuming that hair growth in each area is of equivalent significance and for not considering additional androgen-sensitive areas, such as sideburns and buttocks, which have been added to subsequent versions of the scale.^{13,65–66} In addition, the FG scale fails to consider ethnic variations in hair growth. For example, hirsutism is a less prevalent sign of excess androgens in women from the Shandong region of China. Only 48% of the PCOS patients demonstrated hirsutism compared to other populations where 70–80% of hyperandrogenic women demonstrate hirsutism.^{67–68} Studies of Thai women found that only 2.2% of women evaluated at annual gynecologic examinations had a mFG score of greater than 2 and none had a score greater than 5.⁶⁹ This is compared to studies by DeUgarte where 5.4% of US women had a mFG ≥ 8 .⁷⁰ Studies of Japanese women have also shown a lower prevalence of hirsutism.⁷¹ This is in contrast to studies of PCOS patients from Southern Asia (Pakistani, Bengali, Gujarati or Dravidian Indian), where hirsutism was found to be more prevalent and more severe compared to Caucasians.⁶⁷ These ethnic differences may necessitate the need for different mFG cutoff scores to define hirsutism in different populations and such variations should be considered when clinically evaluating women of different ethnicities.

3. What FG cutoff score should be used to define hirsutism?

There are varied opinions in the literature regarding the appropriate cutoff score to define hirsutism. Some have suggested a score as low as 3 defines hirsutism,⁷⁰ while others use a cutoff of 6.^{14,18,72} The bulk of the literature continues to reference the original FG score of 8–15 as defining mild hirsutism.^{1,4,13,73} This scoring system does not incorporate the impact that unwanted hair has on the

individual patient's well-being and some groups advocate for the use of a quality of life self-assessment.⁷⁴

Primary Evidence

Several studies have evaluated the modified Ferriman-Gallwey scale in which nine areas (upper lip, chin, chest, upper and lower abdomen, thighs, upper and lower back and arms) are evaluated and scored on a scale of 0 to 4 (Figure 8-4).¹ A prospective study by Knochenhauer et al., (1998), screened 369 consecutive women presenting for pre-employment physicals and found that 7.6% of the women had a mFG score of ≥ 6 , 4.6% had a score of ≥ 8 and 1.9% had a score of ≥ 10 .⁴ Based on previous estimates that hirsutism occurs in 5–15% of Caucasian women, the investigators chose to define hirsutism as an mFG score of ≥ 6 .^{2–3} This is consistent with estimates by others that hirsutism affects about 8% of the population of reproductive age women.^{1–2,4}

A prospective observational study of 349 African-American and 278 Caucasian women using the nine-area mFG scale, defined a new mFG score cutoff and demonstrated that no significant difference in prevalence of hirsutism exists between the races.^{62,70} The earlier studies by Hatch defined the mFG cut-off as greater than the 95th percentile. Using those same criteria, this study found an mFG of 7.7 to be the 95th percentile and chose to use an mFG of at least eight to define the upper limit of normal. This corresponded to 5.4% (15 of 278) Caucasians and 4.3% (15 of 349) African Americans, a difference that was not statistically significant. However, the 95th percentile method may not correspond to population or natural cutoffs. When univariate distribution was calculated it was demonstrated that the bulk of the data points were no more than a FG score of 2 and the remainder were at least 3 and it was determined that a mFG of at least 3 was out of the norm in that population. Using the mFG of ≥ 3 , 21.9% (61 of 278) of Caucasians, and 22.6% (79 of 349) of African Americans had scores above this cutoff. Again there was no statistically significant difference between the two races. The authors suggest that a mFG cutoff score of 2 is appropriate based on similar findings in a study of Dutch women that determined a score of 2 or more when evaluating upper lip, sideburns, chest, lower back, lower abdomen, thighs, and arm was abnormal.⁷⁵ In addition, they reported that 69.3% of women who had a score greater than 3 considered themselves hirsute. In contrast, only 15.8% of the women with scores below three considered themselves hirsute. When an mFG score of eight was evaluated it was found that 70% of the women considered themselves hirsute. Based on these results the authors suggested that an mFG of at least 3 is consistent with the population that considers their hair growth to be out of the norm. This study did not correlate mFG scores to serum androgen levels. The women studied were questioned about hair removal and camouflage techniques. The authors estimate that the diagnosis of

hirsutism was missed in 4% of women because of prior hair removal when using a cutoff score of 3. However, if a cutoff score of 8 was used the number of women potentially missed was approximately 50%.⁷⁰

In an additional study of 228 consecutive patients complaining of unwanted hair growth with a mFG score between 1 and 5, it was determined that 55% had androgen excess and would have been missed using a cutoff of 6-8.⁷⁶ As mentioned above, the prevalence and degree of hirsutism varies among ethnicities, and mFG cutoff scores have not been clearly defined for specific populations.⁷¹

Consensus Reports and Clinical Guideline Recommendations

The American Society for Reproductive Medicine advocates the use of a modified Ferriman-Gallwey Index that includes 12 areas: upper lip, sideburn area, chin, lower jaw and upper neck, upper back, lower back, arm, thigh, chest, upper abdomen, lower abdomen and perineum. The practice guidelines do not recommend a cutoff score to use for further evaluation of hirsute patients.²⁷ Other sources citing use of this same modified FG Index report using a score of 8-15 as mild hirsutism, as originally described by Ferriman and Gallwey.⁷³

The Endocrine Society Task Force recommends the use of an mFG scale with the original nine body areas, although they acknowledge the limitations of this scoring system. They recommend using a score of 8-15 to define mild hirsutism and ≥ 15 to define moderate to severe hirsutism.³⁹

The 2009 European Consensus Practice Guidelines recommend use of the mFG index evaluating nine areas and a score of ≥ 8 as defining hirsutism.⁵⁷

A recent systematic review on scoring hirsutism recommends that an mFG score $\geq 6-8$ is appropriate for most populations, with the exception of Mongoloid races. An mFG $\leq 2-3$ may reflect what is considered a “normal” amount of hair. However, for those women with an mFG of 3-5, up to 50% will have an androgen excess disorder.^{63,76}

4. What are the key elements of a focused history and physical exam when evaluating a patient for hirsutism?

Recommendations by experts, and guidelines published by the American College of Obstetricians and Gynecologists, the American Society for Reproductive Medicine, the Endocrine Society and the European Consensus Practice Guideline all concur that an appropriate history and physical examination are key factors in directing subsequent evaluation of hirsutism including laboratory workup and imaging.^{14,27,39,57,77}

A focused history (Table 8-1) should begin with the age of onset, progression, sites of hair growth, psychosocial impact, and treatments used to date. A rapid speed of progression should raise suspicion for androgenic tumors as should symptoms of virilization such as increased libido, deepened voice, or clitoromegaly. A history of galactorrhea is suspicious for hyperprolactinemia and visual disturbances and headaches may be associated with pituitary tumors. It is also important to obtain a current and past medication list (Figure 8-3). Menstrual and fertility history and weight gain are important because non-neoplastic causes of hirsutism most commonly manifest around puberty or following a period of weight gain. A family history of hirsutism or its associated etiologies including PCOS, androgenic alopecia, type II diabetes, early male pattern baldness, and NCAH should be specifically evaluated. Glucose intolerance should be considered if the patient reports polydipsia or polyuria. Cushing syndrome features include mood or sleep changes, weight gain, proximal muscle weakness, excessive thirst, or striae.^{57,73}

A focused physical examination (Table 8-2) should include an assessment of facial and body hair with an mFG scale. Excess androgens may also lead to acne, seborrhea, and patterned alopecia. These clinical findings constitute “SAHA syndrome” (seborrhea, acne, hirsutism and alopecia), a descriptive constellation of clinical features.⁷⁸ Height, weight, and body mass index should be obtained. Central obesity is commonly associated with PCOS and Cushing syndrome. Skin should be evaluated for acanthosis nigricans, more commonly seen in PCOS and HAIRAN syndrome, but also in hyperthecosis, Cushing syndrome, acromegaly, and occasionally NCAH. Clinical evidence of virilization and abdominal and pelvic exams are key indicators for androgenic tumors. Coarse facial features and large hands are indicative of acromegaly. As noted above galactorrhea and visual field testing are important for the diagnosis of hyperprolactinemia and pituitary tumor, respectively. Cushing syndrome features are hypertension, proximal muscle weakness, moon facies, central obesity, striae, and cutaneous infections.^{57,73}

5. What laboratory test(s) should be used in the initial screening of women diagnosed with hirsutism?

Hirsutism by itself is a purely clinical diagnosis and the purpose of further testing is to identify the etiology and associated comorbidities for management, not to confirm the diagnosis of hirsutism (Figure 8-2). Again, based on expert opinion and published Practice Guidelines, the decision to pursue laboratory testing is made based on the mFG score in the context of the history and physical examination findings (Table 8-3). Hirsutism is not always associated with elevated androgen levels, and the underlying cause

TABLE 8-3—Evidence-based First Line and Advanced Testing for Hirsutism and Its Various Etiologies

Etiology	First line	Advanced testing
Hirsutism • FG≥8 (debatable) • FG<15 (i.e moderate severity) • Rapid progression, sudden onset, signs of virilization, clitoromegaly, menstrual irregularity, infertility, acanthosis nigricans, central obesity	AM total testosterone	Free testosterone (preferred if available)
PCOS	DHEAS, 17-HP, PRL to rule out other etiologies	Lipid panel, fasting glucose/insulin, OGTT
NCAH	Am follicular phase 17-HP	ACTH stimulation test
Cushing's syndrome	24 hr urine cortisol	Dexamethasone suppression test (higher false positive rate than 24 hr urine) Lipid panel fasting glucose/insulin, OGTT, potassium ACTH stimulation test (determines ACTH dependent vs. independent Cushing's)
Hyperprolactinemia	Prolactin	CNS imaging if signs and symptoms warrant
Thyroid dysfunction	TSH, T4	Anti-microsomal antibodies
Acromegaly	Somatomedin C(IGF-1)	GH suppression after a glucose load CNS imaging if signs and symptoms warrant
Pituitary, ovarian, adrenal tumor	Androstenedione, DHEAS	MRI

does not always alter management. However, hirsutism may be an identifiable indicator of a medical disorder that does require a specific treatment or assessment. All women with amenorrhea of reproductive age should be initially screened for pregnancy with a urine or serum beta-HCG. A list of laboratory and imaging tests that may be used to evaluate hirsute women along with normal reference ranges is summarized in Table 8-4.

A prospective study of 350 women complaining of hirsutism or androgenic alopecia were tested for serum testosterone, androstenedione, DHEAS, SHBG, LH, follicle stimulating hormone (FSH), 17-hydroxyprogesterone (17-HP), and prolactin (PRL) and a pelvic ultrasound (US) was performed in order to determine the necessity for routine biochemical testing in such women. Clinical assessment along with measurement of serum testosterone as part of the baseline assessment was shown to be sufficient for excluding enzyme deficiencies and virilizing tumors.⁵⁰ PCOS was the most common etiology identified (81% of women with irregular cycles and 52% of women with regular cycles). Only 13 women in total had a significantly elevated baseline testosterone. Eight patients had an endocrine disorder or virilizing tumor.⁵⁰

A large prospective study of 873 women with androgen excess found that only 7% had a specific identifiable disorder such as NCAH, HAIRAN syndrome or

androgen-secreting tumor.¹⁸ The positive predictive value of total testosterone >200 ng/dL has been shown to be low (approximately 10%),⁷⁹ but it is suggested that total testosterone may aid in the diagnosis of some patients with androgen secreting tumors that are less obvious clinically.¹⁸ Additional studies with similar results have also demonstrated that the prevalence of serious endocrine disease causing hirsutism is low, and they are largely apparent on history and clinical examination alone.^{22,51}

Total Testosterone

From a technical perspective, testosterone assays have excessively broad normal ranges and are therefore, often difficult to interpret. The excessively wide reference ranges are likely attributed to the fact that the normative values derived from the “general population” includes women with undiagnosed excess androgens.⁸⁰ Ideally, total testosterone should be tested in the early morning on days 4-10 of the menstrual cycle, because this is how the normal values were established. Specialty laboratories with validated assays allow for more accurate measurements and should be used when available.⁸¹ It should be noted that patient’s taking oral contraceptives would have a falsely low testosterone level. A normal level of total testosterone cannot be used to rule out androgen excess. If this value

TABLE 8-4—Laboratory and Imaging Testing for Women with Hirsutism

Simple Screening Tests	Clinical Information	Normal Values
Total Testosterone	AM level on D 4-10 of menstrual cycle. Levels vary by ~25% with phase of menstrual cycle.	<12 y: 0-100 ng/dL. >12 y: 25-125 ng/dL Tumor work-up indicated if >200 ng/dL
T-SHBG ratio (free testosterone)	The ideal measure for biologically active testosterone.	>18 y : 30-135 nmol/L
DHEA-S	Adrenal androgen. Highest levels are in the morning. Levels affected by stress and exercise.	<12 y: 10-60 mcg/dL >12-35 y: 35-430 mcg/dL Rule out tumor if >600 mcg/dL
Androstenedione	Levels fluctuate widely, hence not measured routinely in the initial evaluation.	Adult women: 30-200 ng/dL Rule out tumor if >500 ng/dL.
<i>Extensive evaluation</i>		
17-OH Progesterone	Screening test for CAH. Early AM measure during the early follicular phase (between D 1-14 of menstrual cycle).	Follicular phase: 20-100 ng/dL. >200 ng/dL strongly suggests NCAH ACTH stimulation testing can confirm the diagnosis
Dihydrotestosterone		Adult women: 6-33 ng/mL
FSH*	Elevated in ovarian failure.	Follicular phase: 2.5-10.2 mU/mL Mid cycle: 3.4-33.4 mU/mL Luteal phase: 1.5-9.1 mU/mL Postmenopausal: 23.-116.0 mU/mL
LH*	An LH:FSH ratio >2 is suggestive but not diagnostic of PCOS.	Pre-menopausal: 2-15 mU/mL Follicular phase: <1-18 mU/mL Mid cycle: 22-105 mU/mL Luteal phase: 0.4-20 mU/mL Post-menopausal: 16-64 mU/mL
Serum estradiol	Should be measured in the setting of oligo/anovulation to rule out hypogonadotropic hypogonadism.	Early follicular phase: 30-100 pg/mL Late follicular phase: 100-400 pg/mL Mid cycle: 90-500 pg/mL Luteal phase: 50-300 pg/mL Post-menopausal: 0-40 pg/mL
Serum prolactin	Elevated in prolactinoma, acromegaly, thyroid disorders, PCOS and with certain medications like opiates and risperidone.	Non-pregnant women: 2-23 ng/mL Pregnant women: 10-209 ng/mL Suspect prolactinoma if: >250 ng/mL Prolactinoma less likely if: <100 ng/mL. Intermediate: >100 ng/mL or <250 ng/mL. The physician must decide whether imaging is indicated.
24 hour urinary free cortisol	Screen for Cushing's syndrome	>50 to 100 mcg/dL in an adult suggests the diagnosis. Three urine free cortisol levels within the normal range are required to exclude Cushing's syndrome
Dexamethasone suppression testing	An abnormal response to the low-dose test may indicate adrenal tumor/ pituitary tumor/ectopic source of ACTH The high-dose test distinguishes a pituitary cause (Cushing's disease) from other causes.	<u>Low dose (1 mg):</u> Overnight: 8 a.m. plasma cortisol <1.8 mcg/dL <u>High dose (8 mg):</u> Overnight: >50% reduction in plasma cortisol Normal suppression is seen with Cushing's disease.
ACTH stimulation test/ Cosyntropin test	Helpful in determining: Acute adrenal crisis Addison's disease (decreased adrenal output) Low pituitary function Pituitary tumors	An increase in cortisol (>18-20 mcg/dL) after stimulation by ACTH is normal, depending on the dose of cosyntropin used.

(Continued)

TABLE 8-4—Laboratory and Imaging Testing for Women with Hirsutism (Continued)

Simple Screening Tests	Clinical Information	Normal Values
Serum ACTH	Higher levels may be due to: Cushing's disease Ectopic tumor producing ACTH Lower levels may be due to: Cushing syndrome related to adrenal tumor Exogenous Cushing syndrome Pituitary insufficiency	8-25 mcg/mL
Combined stimulation test: ACTH and GnRH analogue	Experimental; rarely performed, to evaluate for minor forms of functional ovarian and adrenal hyperandrogenism in patients with idiopathic hirsutism.	
Serum β-HCG	Consider in women of reproductive age presenting with amenorrhea and hirsutism.	Non-pregnant: <3 mU/mL
Imaging		
CT/MRI abdomen/pelvis	To exclude an ovarian or adrenal tumor especially in the presence of virilization or rapid/sudden onset of hirsutism	
Cranial MRI	To exclude pituitary neoplasm if Cushing syndrome, thyroid disease, hyperprolactinemia, acromegaly are suspected.	
Transvaginal ultrasound	Evaluates for polycystic ovaries. Polycystic ovaries are not required for the diagnosis of PCOS nor are they diagnostic (can be seen in CAH)	
Ancillary tests		
Fasting blood glucose	Screening test for type II diabetes.	70-100 mg/dL
Fasting Insulin	For evaluating insulin resistance.	3-19 μ IU/mL
OGTT	An abnormal OGTT requires annual screening with fasting blood glucose to evaluate for development of type II diabetes.	Normal glucose value 2 hours after a 75g load of glucose: <140 mg/dL Abnormal if 2-hour serum glucose \geq 200 mg/dL
Hemoglobin A1c	An early indicator of glucose tolerance.	<7%
Lipid panel	Screen for Hyperlipidemia	TC < 200 mg/dL TG < 150 mg/dL HDL < 40 mg/dL LDL < 100 mg/dL
Potassium levels	Patients with Cushing syndrome can develop hypokalemia and hypokalemic metabolic acidosis.	3.6-5.2 mmol/L
WBC count	Elevated in Cushing syndrome due to effects of cortisol on marginated leukocytes.	3200-10,600 cells/ μ L
IGF-1/Somatomedin-C	Screen for acromegaly.	12 to 15 yrs. 261-1096 ng/mL 16 to 24 yrs. 182-780 25 to 39 yrs. 114-492 40 to 54 yrs. 90-360 55 + yrs. 71-290 80 yrs. 1-71
Serum Growth Hormone	To evaluate acromegaly	0-6 years: 0.10-8.80 ng/mL 7-17 years: 0.06-23.80 ng/mL 18 years and older: 0.03-10.00 ng/mL
TSH, T4, antimicro-somal antibodies	To screen for thyroid disease.	TSH: 0.3-5.0 mIU/L T4: 5.0-12.5 ug/dL

*Note normal reference lab values vary by laboratory.

SHBG, sex hormone binding globulin; DHEA-S, dehydroepiandrosterone sulfate; FSH, follicle stimulating hormone; LH, luteinizing hormone; ACTH, adrenocorticotrophic hormone; GnRH, gonadotropin releasing hormone; HCG, human chorionic gonadotrophin; CT, computer tomography; MRI, magnetic resonance imaging; OGTT, oral glucose tolerance test; TC, total cholesterol; TG, triglyceride; HDL, high density lipoprotein; LDL, low density lipoprotein; WBC, white blood cell; IGF-1, insulin-like growth like factor-1; TSH, thyroid stimulating hormone; T4, thyroxine.

is normal, but the patient has progression of hirsutism or risk factors for hyperandrogenism, then an early morning total and free testosterone should be measured in a reliable specialty laboratory. Normal ranges vary by laboratory and assay method, but normal is approximately 0-100 ng/dL (0.21-2.98 nmol/L). A cutoff value of 200 ng/dL is frequently used as the threshold above, which evaluation for androgenic secreting tumors is warranted.

Free Testosterone

Free testosterone is the biologically active form in the body and the measurement of serum free testosterone is 50% more sensitive than total testosterone in detecting elevated androgen levels.⁸²⁻⁸⁴ Free testosterone was shown by one retrospective study of over 800 hyperandrogenic women to be the solely elevated marker in 15% of cases.¹⁸ Most testosterone is bound to sex hormone-binding globulin (SHBG). Because of this, some women may have levels of testosterone within normal limits, but because of low levels of SHBG, still have elevated levels of free testosterone.⁸⁴ For example, SHBG levels can be suppressed in states of hyperinsulinemia and hyperandrogenemia.⁹ Normal values vary by assay method used and by laboratory, and therefore individual laboratory reference ranges should be used. Normal values also vary by population (pre vs. postmenopausal).⁸²

Unfortunately, testing methods for free testosterone are not as accurate as those for total testosterone and are not as widely available. There is no uniform standard for determining free testosterone, and there is large variability among assays.⁸²⁻⁸⁴ Currently, the most accurate method is to calculate the free testosterone from measurements of both total testosterone and SHBG using the law of mass action, however, the accuracy of this calculation is dependent on the assay methods used to measure the total testosterone and SHBG.⁸⁵⁻⁸⁶ This method was shown to correlate well with the values obtained by equilibrium dialysis ($r=0.99$; $P<0.0001$).⁸² Equilibrium dialysis is labor-intensive and expensive and typically only performed in specialty laboratories.⁸⁷ Assays to measure free testosterone directly have proven to be inaccurate and are not used.⁸⁶

Dehydroepiandrosterone Sulfate (DHEAS)

Dehydroepiandrosterone sulfate is produced almost exclusively by the adrenals and can serve as a marker of adrenal hyperandrogenism. A retrospective study of over 800 hyperandrogenic women found that DHEAS was the sole abnormality detected in 17% of the studied women.¹⁸ Elevated levels of DHEAS in conjunction with clinical findings of a rapid onset or progression of hirsutism and signs of virilization are associated with an increased likelihood of malignancy and warrant additional evaluation with abdominal CT or MRI.^{51,79,88} Adrenal tumors should be suspected if the DHEAS level is greater than 600 mcg/mL

and testosterone level is greater than 200 ng/dL.⁸⁹ However, 10% of androgen producing adrenal tumors do not present with levels to this extreme.¹³ In a retrospective study of 14 women, an elevated total testosterone and/or DHEAS level was able to detect all 14 women with adrenal carcinoma or adenoma. The combined test sensitivity was 100% (95% CI, 77-100) with a specificity of 50% (95% CI, 38-62) for detection of adrenal tumors.⁵¹ One caveat to note is that DHEAS levels decline with age suggesting a need for age-related normative values.⁹⁰

Androstenedione

Androstenedione along with testosterone and DHEAS may help to predict the source of excess androgen. If the testosterone and androstenedione levels are elevated, but the DHEAS level is within normal limits, then the ovaries are the likely source of excess androgen.⁹¹ A prospective study of 350 hirsute women demonstrated that the measurement of androstenedione in conjunction with total testosterone did not aid in identifying or excluding disorders.⁵⁰ Androstenedione is not routinely used in the initial evaluation of hirsutism by many clinicians because its concentration can fluctuate widely, even in normal women and there is little direct evidence to support obtaining this laboratory value.⁹¹

Consensus Report and Clinical Guideline Recommendations

The 2009 European Consensus Clinical Practice Guideline recommends using free testosterone determined by measuring both total testosterone and SHBG (calculating the free androgen index [FAI] by dividing total testosterone by SHBG level and multiplying by 100) to assess hyperandrogenemia in women with a FG score of at least 8. For women with a FG score greater than 15 they describe free testosterone evaluation as “prudent.” The guidelines do not recommend the use of serum total testosterone alone because it has a low sensitivity for the diagnosis of PCOS, failing to detect 20-40% of PCOS cases.⁹²⁻⁹³ The guidelines do recommend additional testing for thyroid function, serum prolactin, serum 17-HP, and 24-hour urine cortisol as warranted by clinical suspicion in women with either mild ($FG>8$) or moderate ($FG>15$) hirsutism. If patients have a testosterone level greater than 1.5-2 times the upper limit of normal or a history of rapid onset of virilization, they recommend additional testing with DHEAS and androstenedione to identify an adrenal or ovarian source, respectively. Pelvic ultrasound is recommended as a useful screen for both PCOS and neoplasms, when suspected based on history and clinical symptoms.^{34,57}

The 2008 Endocrine Society Clinical Practice Guideline does not suggest testing for elevated androgen levels in women with isolated mild hirsutism (mFG 8-15), because

they describe the likelihood of uncovering a diagnosis that would alter management or outcome as low.³⁹ They do, however, suggest testing androgen levels in women with moderate to severe hirsutism, or any degree of hirsutism that is associated with a sudden onset, rapid progression or menstrual irregularity, infertility, central obesity, acanthosis nigricans, or clitoromegaly. These guidelines are considered weak recommendations by the task force and were based on “very low quality evidence” according to the guideline. Because of the weak evidence to support these recommendations, the task force recommends that patients’ circumstances, values, and preferences be evaluated before testing decisions are made. These recommendations are based on the following evidence: in approximately one-half of women with mild hirsutism (FG score of 8-15), elevated androgen levels are not found. However, in the other half and in women with moderate to severe hirsutism (FG score >15), the measured levels of both total and free testosterone are found to be elevated.^{18,89} If testing is deemed warranted they recommend an early morning plasma testosterone level as the initial test with the addition of an early morning follicular phase 17-HP for women at high risk for NCAH.³⁹ They do note that if the measurement of free testosterone could be done reliably and was less costly, they would recommend plasma-free testosterone as an initial test for hyperandrogenism in all hirsute women.³⁹

The 2006 American Society for Reproductive Medicine Guidelines recommend testing for total and free testosterone, DHEAS and morning follicular phase 17-HP for patients suspected to have androgen excess based on mFG scale and physical examination findings.²⁷

The 2002 Clinical Management Guidelines from the American College of Obstetricians and Gynecologists recommend that because of the high frequency of association between hirsutism and PCOS, along with the significant medical risks linked to PCOS, an evaluation of testosterone and 17-HP in patients presenting with hirsutism and menstrual irregularities is recommended.⁹⁴

6. What additional testing is recommended for the diagnosis of PCOS and what ancillary tests should be done for these patients?

Based on a review of the literature and consensus conference, the 2009 Androgen Excess and PCOS (AE-PCOS) task force defined criteria for PCOS by hyperandrogenism (clinically or biochemically), ovarian dysfunction (menstrual irregularities or polycystic ovaries) and the exclusion of other related disorders.³³ An LH:FSH ratio greater than 2:1 has limited sensitivity and is no longer part of the criteria for diagnosis of PCOS.³⁴ Polycystic ovaries visualized by ultrasound are considered a diagnostic marker of PCOS by the American Society for Reproductive Medicine, but are not required for the diagnosis and are not specific to PCOS.³⁴

In women diagnosed with PCOS, a fasting lipid profile, fasting serum glucose, fasting serum insulin, and glucose tolerance test should be obtained to identify abnormalities in glucose metabolism, hyperlipidemia, and hyperinsulinemia. Calculation of BMI for these patients is also recommended because of the prevalence of central obesity in PCOS.⁵⁷ Patients with abnormal glucose tolerance tests need to be followed annually because of the risk for progression to diabetes, which has been demonstrated to be 3-7 times greater in women with PCOS.^{27,39,95} Based on the WHO diabetes criteria, a study evaluating 254 women with PCOS found that, 31.1% demonstrated glucose intolerance and 7.5% had diabetes. This is significantly higher than control women ($p=0.001$; odds ratio (OR) = 2.76 (95% CI, 1.25-6.57)).⁹⁶

A retrospective study of women with PCOS in the United Kingdom, demonstrated that all cause cardiovascular mortality was similar between women with PCOS and controls, however, risk factors for cardiovascular disease were increased (i.e., diabetes (OR 2.2 (0.9-5.2)); hypertension (OR 1.4 (0.9-2.0)); and hypercholesterolemia (OR 3.2 (1.7-6.0)) (Figure 8-2).⁹⁷ Furthermore, total cholesterol and low density lipoprotein levels were increased in obese PCOS women compared to obese controls (mean difference of 29 mg/dL (95% CI, 14-45 mg/dL; $P < 0.001$).⁹⁸ Similar results were found in nonobese women with PCOS compared to nonobese controls.⁹⁸ Insulin resistance was shown to increase with BMI in women with PCOS and overweight PCOS patients are more likely to suffer from menstrual irregularities than their “lean” PCOS counterparts.^{95,99-100}

Polycystic ovary syndrome is inherited in an autosomal dominant pattern with 90% penetrance.⁵⁵ Male pattern baldness prior to age 30 was shown to be a useful phenotypic predictor for male carriers.⁵⁵ Men with premature male pattern balding were shown to have elevated testosterone levels when compared to controls ($P=0.02$). These men may also develop insulin-resistance and increased body hair secondary to elevated androgen levels.³¹⁻³²

7. When should *nonclassical adrenal hyperplasia* (NCAH) be suspected and what tests are used for screening and diagnosis?

Nonclassical adrenal hyperplasia cannot reliably be distinguished clinically from other causes of hyperandrogenism. Like PCOS, these patients are likely to present peripubertally with mild to moderate hirsutism, acne, or oligomenorrhea, and have subsequent studies revealing elevations in testosterone, DHEAS and androstenedione along with polycystic ovaries detected by ultrasound in some patients.¹⁰¹ It has been demonstrated that the mean levels of androstenedione are higher in NCAH than in controls, but there is significant overlap with PCOS, which limits the diagnostic value of this finding.⁴⁶ Even in the setting of a normal serum total testosterone, the diagnosis of NCAH

should be pursued in certain high-risk hirsute populations (i.e., those with a family history of CAH or women of certain high-risk ethnicities [Ashkenazi Jews 1:27; Hispanics 1:40; Slavics 1:50; compared to US Caucasians 1:1000 and African-Americans rare]). Correctly diagnosing NCAH in hyperandrogenic women is important for several reasons: (1) patients with severe CYP21 alleles may require genetic counseling because of the risk of delivering a child with classic congenital adrenal hyperplasia (CAH); (2) women with CAH and male and female carriers have an increased risk for developing adrenal adenomas and incidentalomas; (3) early treatment with OCPs protects the ovaries from becoming polycystic and sclerotic; and finally (4) the choice of infertility treatment for adult women with NCAH varies from PCOS, with glucocorticoid therapy often restoring ovulation.²³

Primary Data

In a recent prospective study of 270 women in Spain with hyperandrogenic complaints, it was demonstrated that screening for NCAH with serum androgen tests alone has poor specificity.²³ The preferred screening test for CAH is an elevated early morning 17-HP. A random test of 17-HP may be normal. A study by Azziz et al. demonstrated that a basal 17-HP level of less than 2 ng/mL could be used to rule out NCAH with a NPV of almost 100%.⁴⁶ A subsequent study of 266 hyperandrogenic women reported that follicular phase samples have a higher specificity and a lower false-positive rate than luteal phase samples and that obtaining a morning sample is essential, because 5-15% of the cases of NCAH would have been missed if afternoon samples were used.¹⁰²

In the previously mentioned Spanish study, it was demonstrated that a single basal serum 17-HP test has a 0.97 (95% CI; 0.934-1.008) chance of detecting NCAH in hyperandrogenic women using the Immuchem 17-HP RIA assay. The 17-HP cutoff value recommended by this study is 1.7 ng/mL or greater based on 100% sensitivity and 88.6% specificity. This value is lower than the 2 ng/mL value recommendation by the Endocrine Society, which corresponds to a sensitivity of 83.3% and 93.6% specificity.²³ The authors argue that reaching 100% sensitivity for the screening test is important because proper diagnosis is important for both genetic counseling and infertility treatment. Further confirmatory testing requires an ACTH stimulation test (measurement of 17-HP level after administration of an IV bolus of ACTH).⁴⁶ A cutoff of ≥ 10 ng/mL has been shown to be consistent with women subsequently confirmed to have NCAH by genetic analysis of CYP21.^{23,46,103}

Consensus Report and Clinical Guideline Recommendations

Both the Rotterdam guidelines and the European Consensus report include 17-HP in the initial recommended laboratory

investigations for screening of NCAH in hyperandrogenic women.⁵⁷

In high-risk populations, the Endocrine Society Task Force recommends measuring an early morning 17-HP during the follicular phase of the menstrual cycle.³⁹ If the 17-HP is greater than 2 ng/mL, then an ACTH stimulation test should be performed. If the 17-HP is greater than 10 ng/mL after ACTH stimulation the diagnosis of NCAH is confirmed.^{46,102}

8. Which tests are used to differentiate HAIRAN syndrome from PCOS and what ancillary tests need to be performed after the diagnosis?

The clinical presentation of HAIRAN syndrome can mimic androgen-secreting tumors and therefore, the latter must be excluded. HAIRAN is characterized by extremely high insulin levels, but may be difficult to differentiate from PCOS, with which it has significant clinical overlap. This syndrome can be confirmed by measuring the basal insulin level and serum glucose and insulin after a glucose tolerance test. Patients with HAIRAN typically have a basal insulin level greater than 80 uU/mL if fasting and greater than 500 uU/mL after glucose challenge.^{42,104} Prospective studies by Azziz et al. demonstrated that HAIRAN patients had higher fasting insulin ($88.1\mu\text{M}/\text{mL} +/- 4.5$) compared to PCOS ($21.1\mu\text{M}/\text{mL} +/11.0$).¹⁸ Another recent study showed that the degree of fasting hyperinsulinemia had the greatest amount of influence on the severity of hirsutism when compared to testosterone and 17-HP serum levels (Spearman correlation 0.175; Spearman P value 0.0006).⁷²

Women diagnosed with HAIRAN syndrome should receive a lipid panel and HbA1c because of their increased risk for hyperlipidemia and diabetes. They are also at increased risk for cardiovascular disease, hypertension, and infertility. Due to its significantly higher associated morbidity, the American Society for Reproductive Medicine emphasizes the need to differentiate HAIRAN syndrome from PCOS.²⁷

9. What are the clinical indicators for androgenic neoplasms and what studies are used to confirm the diagnosis?

Primary Evidence

Androgenic neoplasms are a rare, but serious cause of hirsutism and hyperandrogenemia. Sudden onset and rapid progression of hirsutism, signs, and symptoms of virilization and palpable abdominal or pelvic masses are clinical indicators for an androgenic neoplasm. Two studies have examined the utility of elevated androgen levels at identifying an androgenic neoplasm. The first study examined 14 hirsute women with histologically proven adrenal tumors

compared to 73 women with hirsutism of non-neoplastic etiology. An elevated serum total testosterone or DHEAS had a 100% sensitivity (95% CI, 77-100) and specificity of 50% (95% CI, 38-62) at detecting adrenal neoplasms. Further testing with dexamethasone suppression reduced DHEAS and urinary 17-ketosteroid (testosterone metabolite, Figure 8-1) values to within the normal range only in women with non-neoplastic hirsutism (sensitivity 100% (95% CI, 74-100); specificity 100% (95% CI, 89-100) for detecting adrenal tumors). They conclude that serum testosterone and DHEAS are appropriate initial tests for detecting an androgenic tumor, and that a positive response to dexamethasone suppression in those identified to have elevated values can virtually rule out an underlying adrenal tumor as the cause.⁵¹

A second study over a 10-year period examined 478 hyperandrogenic women (defined by total or free testosterone or DHEAS >95th percentile of controls). Eighty percent of these women also had hirsutism (defined by FG ≥6). Overall, 11 or 2.3% of the patients had a total testosterone >250 ng/dL (8.7 nmol/L), and only one of these patients had an androgen-secreting neoplasm. Based on these findings a testosterone level >250 ng/dL was 100% sensitive and 98% specific. The NPV was 100%, but the PPV was only 9%. None of the patients had a DHEAS >600 ng/mL. The authors suggest that testosterone and DHEAS are not a cost-effective method for screening of these tumors in unselected hyperandrogenic women because of the low frequency of the disorder. They recommended testing serum androgens when a neoplasm is suspected based on clinical evaluation.⁷⁹

Consensus Report and Clinical Guideline Recommendations

The Endocrine Society Clinical Practice Guidelines recommend evaluation for androgenic tumors, when there is sudden onset and rapidly progressive hirsutism along with evidence of virilization. They recommend a pelvic ultrasound, serum testosterone, serum androstenedione and serum DHEAS, followed by a CT of the abdomen and pelvis if a tumor remains suspected. They do not identify reference ranges and cut-off values for the serum androgens, but they do acknowledge that height of the androgen levels has a poor predictive value unless testosterone level is very high (adult male range) or DHEAS >700 µg/dL, both of which are described as useful predictors of an androgenic tumor.³⁹

The European Consensus Guidelines recommend that patients presenting with testosterone levels greater than 1.5-2 times the upper limit of normal (70-90 ng/dL defined as normal), those with rapid onset of hirsutism, or those with evidence of virilization, should have DHEAS and androstenedione levels measured to identify

the source of hyperandrogenemia as either adrenal or ovarian, respectively. They also recommend ultrasound of the ovaries and adrenals as a useful tool when findings suggest an underlying neoplasm. When possible, transvaginal ultrasound is the preferred method for evaluation of the ovaries.⁵⁷

10. Who should be evaluated for Cushing syndrome?

Patients with hypertension, fat redistribution (dorsocervical fat pad, moon facies, central adiposity, and slim limbs), purple striae, hyperpigmentation, menstrual irregularities, cutaneous fungal and bacterial infections, and proximal muscle weakness should be evaluated for Cushing syndrome. Cushing syndrome is a rare cause of hirsutism with prevalence reported to be 0-1% in hirsute women.^{20,50} Cushing syndrome is screened for with a 24-hour urine cortisol and an overnight dexamethasone suppression test with a fasting early morning cortisol. The overnight dexamethasone suppression test involves administering 1 mg of dexamethasone at 11 p.m. and then measuring the plasma cortisol in the fasting patient the following morning at 8 a.m. The plasma cortisol value should be <1.8 mcg/dL (normal values vary). Urine cortisol is the most specific test for Cushing, with a value greater than 50-100 mcg/dL (normal values vary between labs) being diagnostic. In order to exclude Cushing syndrome, the urine cortisol test must be negative three times. Twenty-four hour urinary cortisol has a 95-100% sensitivity and specificity. A dexamethasone suppression test is only 80% specific, leading to many false positives that need to be confirmed by 24-hour urine cortisol test.¹⁰⁵ Further testing can be performed to determine if the disease is ACTH-dependent or independent, with ACTH-dependent Cushing being more likely to cause hyperandrogenemia.

Patients found to have Cushing syndrome should also have a fasting blood glucose, glucose tolerance test, lipid panel, and potassium level because of their increased risk for cardiovascular disease and hypokalemia. They are also at risk for osteoporosis and glaucoma, which may warrant additional screening tests (Figure 8-2).^{73,106-107}

Consensus Report and Clinical Guideline Recommendations

The American Society for Reproductive Medicine recommends the use of the dexamethasone suppression test or a 24-hour urine cortisol if Cushing syndrome is clinically suspected.²⁷

The European Consensus Guideline recommends a 24-hour urine cortisol test as part of the investigation of hirsute women, if there is clinical suspicion of Cushing syndrome.⁵⁷

11. Is hypothyroidism associated with hirsutism and how should it be evaluated?

Hypothyroidism should be suspected in a hirsute patient if they also present with diffuse alopecia, weight change, or cold intolerance. On physical examination, a goiter may be detected. Additional diagnostic testing should include TSH, free T4, and thyroid antimicrosomal antibodies. There is little evidence to suggest an association of thyroid disease and hirsutism other than a single report of a higher incidence of thyroid disease (55%) in patients with "idiopathic" hirsutism compared to control patients (12.5%).¹⁰⁸ This is contradictory to studies by Ferriman and Purdie¹⁰⁹ and Azziz et al. who reported 0 of 467 hirsute women and 1 in 873 women with androgen excess, respectively, were found to have hypothyroidism (although 5 of the 873 had been previously diagnosed).¹⁸ Both groups reported that the prevalence of thyroid dysfunction in hirsute and hyperandrogenic women studied was actually less than the prevalence reported in the general population.¹¹⁰ Despite the low yield for identifying an etiology for hirsutism, the 2003 Rotterdam PCOS Consensus contends that it is still reasonable to test because thyroid disease screening is advised for all women of reproductive age.⁴⁰

12. When should patients be evaluated for acromegaly?

Acromegaly is a rare cause of hirsutism and is the result of unregulated oversecretion of growth hormone (GH) most often caused by a pituitary adenoma.¹¹¹ Prolonged exposure to elevated levels of GH and its target hormone, insulin-like growth factor-1 (IGF-1), results in tissue enlargement and metabolic abnormalities, including insulin resistance leading to glucose intolerance and diabetes. GH and SHBG levels are inversely correlated ($r = -0.6$; $P < 0.01$) in patients with acromegaly.¹¹² The decrease in SHBG and resultant increase in free testosterone contributes to menstrual irregularities (reported in 81% of patients), and hirsutism, (noted in 55%).¹¹² Characteristic physical findings include coarse facial features, large hands, acanthosis nigricans, pigmented skin tags, and hyperhidrosis. Patient morbidity and mortality are increased because of increased risk of colorectal cancer and cardiovascular disease related to cardiomyopathy, hypertension, and diabetes (Figure 8-2). Somatomedin C (IGF-1), which is GH dependent, is the preferred screening test (normal values vary by age). Serum somatomedin C is elevated in almost all acromegalic patients, but uncontrolled diabetes, starvation, and liver failure can lead to falsely low values. In these cases, a serum GH level after a glucose load can be measured. The GH level fails to suppress to $<1\mu\text{g/L}$ in patients with true acromegaly.¹¹³⁻¹¹⁴ 30-40% of acromegalic patients are

also hyperprolactinemic.¹¹² Cranial MRI is subsequently used to identify a possible pituitary tumor.²⁷ Evaluation of somatomedin C (IGF-1) levels is not part of the routine evaluation of hirsute women, and should only be performed in the appropriate clinical context.

13. Are prolactinomas associated with hirsutism and how are they diagnosed?

Hyperprolactinemia is a rare cause of hirsutism as demonstrated by O'Driscoll with 1 in 350 women with hirsutism and/or androgenic alopecia having hyperprolactinemia and by Azziz with comparable findings of 3 in 873 women diagnosed with hyperandrogenemia.^{18,50} In patients with spontaneous or expressible galactorrhea, oligo or amenorrhea, or visual field defects, evaluation of prolactin levels can rule in or out a prolactin-producing pituitary adenoma. A subsequent cranial MRI is useful for confirming the clinical suspicion of a pituitary adenoma.^{27,39} Additional causes of elevated prolactin include PCOS, acromegaly, thyroid disorders, and certain drugs.

Consensus Report and Clinical Guideline Recommendations

The European Consensus Guidelines recommend a prolactin level test to exclude hyperprolactinemia in women with moderate to severe hirsutism.⁵⁷

The American College of Obstetricians and Gynecologists describes hyperprolactinemia as a rare cause of hirsutism, but recommends evaluation of prolactin levels in patients with amenorrhea or galactorrhea.⁹¹

CONCLUSION

Hirsutism affects 5-15% of premenopausal women worldwide and is one of the dermatologic expressions of hyperandrogenemia or of increased peripheral androgen activity. Societal norms of acceptable amounts of excess body and facial hair in women vary among populations. Although most women present only for treatment of the excess hair, there can be significant underlying associated medical disorders (Figure 8-2), that if detected and treated early, can minimize patient morbidity. Therefore, understanding the diagnostic work-up of the hirsute patient and the timing and utility of various hormonal tests is important for optimal patient management (Figure 8-6). The specific hormonal abnormalities that may be seen in the various etiologies underlying hirsutism are summarized in Table 8-5. Evidence related to diagnosis and work-up of hirsutism is generally weak; however, several recent practice guidelines make recommendations in this regard and are excellent resources for further reference on the topic.

Labs	Normal	Normal/elevated	Elevated	Idiopathic	PCOS	HAIR-AN	CAH	Cushing's syndrome	Prolactinemia	Thyroid	Acromegaly	Adrenal Tumor	Ovarian Tumor
Testosterone	Normal	Normal/elevated	Elevated							Normal	Normal/elevated	Elevated	
DHEA-S	Normal	Normal/elevated	Elevated							Normal	Normal/elevated	Elevated	
17-OH Progesterone	Normal	Normal/elevated	Elevated				Normal	Normal/elevated					
LH/FSH	Normal	Normal/elevated	Elevated				Normal	Normal/elevated					
Cortisol	Normal	Normal/elevated	Elevated				Normal	Normal/elevated	Normal	Normal	Normal	Normal	Normal/elevated
Prolactin	Normal	Normal/elevated	Elevated				Normal	Normal/elevated	Normal	Normal	Normal	Normal	Normal

DHEA-S: dehydroepiandrosterone sulfate; 17-OH- Progesterone: 17- hydroxyprogesterone; LH: luteinizing hormone; FSH: follicle stimulating hormone; PCOS: Polycystic ovary syndrome; HAIR-AN syndrome: hyperandrogenism, insulin resistance, acanthosis nigricans; CAH: congenital adrenal hyperplasia.

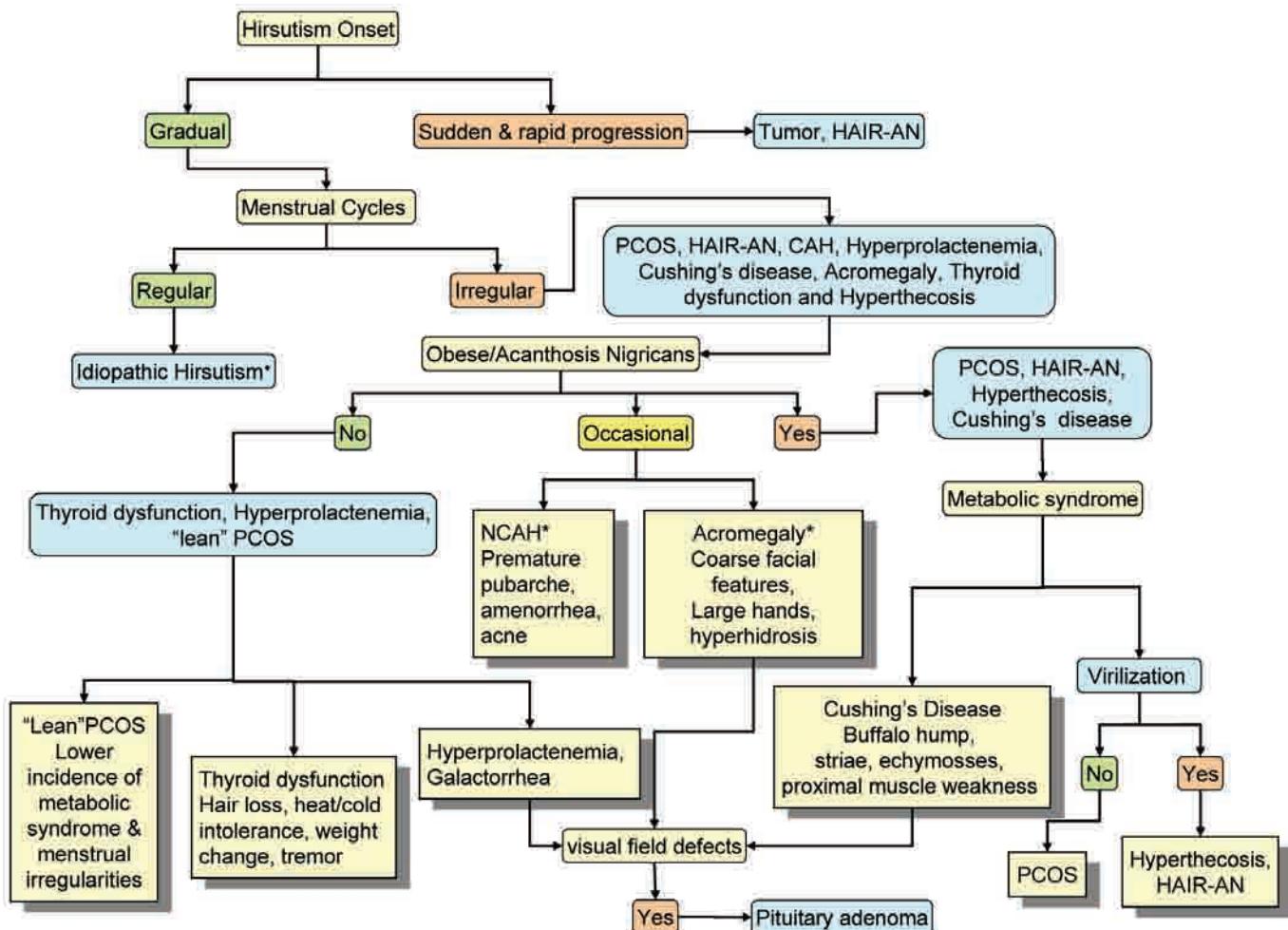


FIGURE 8-6 Evidence based algorithm for the clinical evaluation of hirsutism. HAIR-AN syndrome: hyperandrogenism, insulin resistance, acanthosis nigricans; PCOS: Polycystic ovary syndrome; CAH: congenital adrenal hyperplasia; NCAH: nonclassic adrenal hyperplasia.

What We Know

- Despite limitations, the mFG scale is the standard tool for assessment of hirsutism. Score cutoffs to define hirsutism are largely based on a Caucasian population and may not adequately reflect severity of hirsutism in women of other ethnicities.
- An mFG score of ≥ 8 is commonly used to define mild hirsutism; however, in some populations, approximately 50% of women with a score of 3 to 5 will have an androgen excess disorder.
- There is weak evidence suggesting against testing androgen levels in women with mild hirsutism, because of the low likelihood of uncovering a diagnosis that would alter management or outcome.
- There is consensus that women presenting with signs and symptoms of virilization, those with rapid progression or sudden onset of hirsutism, those with menstrual irregularity or infertility, central obesity, acanthosis nigricans, clitoromegaly, or moderate to severe hirsutism should have androgen levels tested.
- Testosterone is the most recommended first choice test for women presenting with hirsutism. Free testosterone is 50% more sensitive, but is expensive and requires a specialty laboratory test to be measured accurately.
- Clinical assessment including history and physical examination findings are the key determinants for directing more extensive testing and evaluation.
- DHEAS is a marker of adrenal hyperandrogenemia.
- Women with PCOS, require monitoring of glucose, insulin, and lipid levels. Patients with abnormal glucose tolerance tests need to be followed annually because of the risk for progression to diabetes.
- Some cases of “idiopathic” hirsutism may actually be unrecognized PCOS.
- Not all hirsute women have measurable hyperandrogenemia and not all hyperandrogenic women are hirsute. This variability reflects differences in peripheral androgen metabolism.
- Women with NCAH can have a PCOS phenotype. Early morning 17-HP level is the preferred screening test for NCAH.
- HAIRAN patients are at risk for diabetes, hypertension, cardiovascular disease, and infertility and are affected more severely than patients with PCOS.
- Androgenic tumors should be suspected clinically if there is rapid onset of hirsutism and virilization, and biochemically if testosterone levels are 1.5-2 times the upper limit of normal and DHEAS is >600 ng/mL. Visual field defects suggest a pituitary adenoma.
- Cushing syndrome, acromegaly, and prolactinomas are very rare causes of hirsutism.
- The most sensitive and specific screening test for Cushing syndrome is a 24-hour urine cortisol and the next best test is a dexamethasone suppression test.
- Acromegaly is diagnosed by clinical features and elevated somatomedin C levels.
- Clinical features of galactorrhea, oligomenorrhea, or infertility should prompt evaluation for a prolactinoma.
- Although there is poor evidence that hypothyroidism can cause hirsutism, screening is advised for all women of reproductive age and is best done with a TSH, followed by a free T4.

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Therapy



Systematic Review and Meta-Analysis

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EVIDENCE-BASED MEDICINE (EBM)

Evidence-based medicine is defined as ‘the conscientious, explicit, and judicious use of current best evidence in making clinical decisions about the care of individual patients.¹ Practicing EBM is not practicing ‘cook book medicine’, but it encourages clinicians to integrate valid and useful evidence with their clinical expertise and the unique features of their patients. This combination of knowledge should lead to optimal patient care.

To practice EBM there are five steps:

1. Formulate a clear clinical question.
2. Search the literature to identify relevant articles: tracking down the best evidence with which to answer the question.
3. Critically appraise the articles for quality and the usefulness of results. Assess the study’s validity (i.e., closeness to the truth), impact (i.e., size of the effect), and applicability (i.e., usefulness in clinical practice on individual patient level). In this stage recommendations may be formulated.
4. Implement clinically useful findings into practice by integrating the critical appraised findings with our clinical expertise and with our patient’s unique biology, values, and circumstances.
5. Evaluating our effectiveness and efficiency in executing steps 1-4 and seeking ways to improve them both for next time.

In clinical practice, the emphasis on each of the five EBM steps may vary and depends in part on the frequency with which we see patients with a specific disease. Step 4 remains crucial for applying EBM in the treatment of all conditions. For conditions encountered daily (e.g., treatment of mild psoriasis, atopic dermatitis, hand eczema and warts), we need to be up to date in our knowledge and very sure about what we are doing. Step 2 (searching) and 3 (critically appraising) are important operating in this “appraising” mode.

For conditions that we encounter less frequently, sources are searched that have already undergone rigorous critical appraisal such as Cochrane reviews, synthesis in Best Evidence and reviews in the Database of Abstracts of Reviews of Effects (DARE). Databases of pre-appraised

resources increase the feasibility of this approach for busy clinicians. Thus, we look for available appraised evidence and focus on eligibility criteria and critical appraisal procedure used. Therefore, the question ‘can I apply this valid, important evidence to my patient’ (step 4) remains very important in integrating EBM in the care of these diseases.

For rare conditions (e.g., cicatricial alopecia caused by pseudolymphoma), we seek, and are likely to accept and apply the recommendations received from peers with high levels of expertise in this specific condition. This “replicating” mode is blind to whether the advice received from experts is authoritative (evidence based, resulting from their operating appraising mode) or merely authoritarian (opinion based, resulting from pride and prejudice). References and background information of the recommendations received assist to judge the validity of the expert source and opinion.¹

In all circumstances, healthcare professionals should apply their general medical knowledge and clinical judgment in both the assessment of the importance of recommendations and the application of the recommendations. The following questions should be asked when deciding on the applicability of the available evidence to patients:

- Is my patient so different from those in the study that results cannot be applied?
- Is the treatment feasible in my setting?
- What are my patient’s likely benefits and harms from the therapy?
- How will my patient’s preferences influence the decision^{2,3}

In total quality management (TQM) principles, the patient is the main and central customer of the health care system and a patient’s requests and preferences are the first priorities. The goal is to emphasize applicability of EBD facts to a specific patient.

Searching for the best available evidence and analyzing and summarizing the data, which is the essence of a systematic review (SR), is one of the main tools used in EBM. In SRs the level of evidence of the underlying studies will be given, and if recommendations are formulated, the grade of recommendations is provided.

LEVELS OF EVIDENCE AND RECOMMENDATIONS

Currently, a variety of grading systems for evidence and recommendations are being used in EBM. The system used for assessing the level of evidence in a study should be clearly defined. The hierarchy of evidence and the recommendation grading's (based on the available evidence) relates to the strength of the literature and not necessarily to clinical importance.⁴

The hierarchy of studies for obtaining evidence on therapeutic interventions is:

LEVELS OF EVIDENCE

The Levels of Evidence from the Oxford Centre for EBM (May 2001):⁵

- Ia: Systematic review or meta-analysis of randomized-controlled trials (RCT)
- Ib: At least one RCT
- IIa: At least one well-designed controlled study without randomization
- IIb: Controlled observational studies: at least one well-designed quasi-experimental study such as a cohort study or case control studies
- III: Uncontrolled observational studies: well-designed non-experimental descriptive studies such as comparative studies, correlation studies, case-control studies and case series
- IV: Expert committee reports, opinions and/or clinical experience of respected authorities

Expert opinion must not to be confused with personal experience that is sometimes called eminence-based medicine. Expert opinion is the lowest level of evidence in this hierarchy and below experimental evidence but in the absence of experimental evidence may be the best guide available.⁶

Recommendation may be formulated following the hierarchy of the level of evidence of the underlying studies:

GRADING OF RECOMMENDATIONS

- A: Based on hierarchy I evidence
- B: Based on hierarchy II evidence or extrapolated from hierarchy I evidence
- C: Based on hierarchy III evidence or extrapolated from hierarchy I or II evidence
- D: Directly based on hierarchy IV evidence or extrapolated from hierarchy I, II or III evidence

A simpler system of A, B or C is recommended by the US Government Agency for Health Care Policy and Research (AHCPR):⁷

- A: Requires at least one RCT as part of the body of evidence.

- B: Requires availability of well-conducted clinical studies but no RCT in the body of evidence.
- C: Requires evidence from expert committee reports or opinions and/or clinical experience of respected authorities. Indicates absence of directly applicable studies of good quality.

The focus of the above-mentioned grading systems is only applicable for therapeutic interventions. In addition to therapy, Table 9-1 presents also the Oxford levels of evidence of other domains that are important in medicine such as prevention, harm, etiology, prognosis, and diagnosis.

Other systems are available. See also The US task force grading system: *<http://www.uspreventiveservicestaskforce.org/3rduspstf/ratings.htm>*

QUALITY OF EVIDENCE

The U.S. Preventive Services Task Force (USPSTF) grades the quality of the overall evidence for a service on a 3-point scale (good, fair, and poor):

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

STRENGTH OF RECOMMENDATIONS

The USPSTF grades its recommendations according to one of five classifications (A, B, C, D, I), reflecting the strength of evidence and magnitude of net benefit (benefits minus harms).

A.—The USPSTF strongly recommends that clinicians provide (the service) to eligible patients. *The USPSTF found good evidence that [the service] improves important health outcomes and concludes that benefits substantially outweigh harms.*

B.—The USPSTF recommends that clinicians provide (this service) to eligible patients. *The USPSTF found at least fair evidence that (the service) improves important health outcomes and concludes that benefits outweigh harms.*

C.—The USPSTF makes no recommendation for or against routine provision of (the service). *The USPSTF found at least fair evidence that (the service) can improve health outcomes but concludes that the balance of benefit and harm is too close to justify a general recommendation.*

D.—The USPSTF recommends against routinely providing (the service) to asymptomatic patients. *The USPSTF found*

TABLE 9-1—Oxford Center for Evidence-based Medicine Levels of Evidence (May 2001)

TABLE 9-1—Oxford Center for Evidence-based Medicine Levels of Evidence (May 2001)					
Level	Therapy/Prevention, Etiology/Harm	Prognosis	Diagnosis	Differential diagnosis/ symptom prevalence study	Economic and decision analyses
1a	SR (with homogeneity*) of RCTs	SR (with homogeneity*) of inception cohort studies; CDR [†] validated in different populations	SR (with homogeneity*) of Level 1 diagnostic studies; CDR with 1b studies from different clinical centers	SR (with homogeneity*) of prospective cohort studies	SR (with homogeneity*) of Level 1 economic studies
1b	Individual RCT (with narrow Confidence Interval [‡])	Individual inception cohort study with ≥ 80% follow-up; CDR [†] validated in a single population	Validating ^{**} cohort study with good ^{†††} reference standards; or CDR tested within one clinical centre	Prospective cohort study with good follow-up ^{***}	Analysis based on clinically sensible costs or alternatives; systematic review(s) of the evidence; and including multi-way sensitivity analyses
1c	All or none [§]	All or none case-series	Absolute SpPins and SnNouts ^{††}	All or none case-series	Absolute better-value or worse-value analyses ^{††††}
2a	SR (with homogeneity*) of cohort studies	SR (with homogeneity*) of either retrospective cohort studies or untreated control groups in RCTs	SR (with homogeneity*) of Level >2 diagnostic studies	SR (with homogeneity*) of 2b and better studies	SR (with homogeneity*) of Level >2 economic studies
2b	Individual cohort study (including low quality RCT; e.g., <80% follow-up)	Retrospective cohort study or follow-up of untreated control patients in an RCT; Derivation of CDR [†] or validated on split sample ^{§§} or databases only	Exploratory ^{**} cohort study with good ^{††††} reference standards; CDR [†] after derivation, or validated only on split sample ^{§§} or databases	Retrospective cohort study, or poor follow-up	Analysis based on clinically sensible costs or alternatives; limited review(s) of the evidence, or single studies; and including multi-way sensitivity analyses
2c	"Outcomes" Research, Ecologic studies	"Outcomes" Research		Ecological studies	Audit or outcomes research
3a	SR (with homogeneity*) of case-control studies		SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies	SR (with homogeneity*) of 3b and better studies
3b	Individual Case-Control Study		Nonconsecutive study; or without consistently applied reference standards	Nonconsecutive cohort study, or very limited population	Analysis based on limited alternatives or costs, poor quality estimates of data, but including sensitivity analyses incorporating clinically sensible variations.
4	Case-series (and poor quality cohort and case-control studies ^{§§})	Case-series (and poor quality prognostic cohort studies ^{***})	Case-control study, poor or non-independent reference standard	Case-series or superseded reference standards	Analysis with no sensitivity analysis
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"	Expert opinion without explicit critical appraisal, or based on physiology, bench research or "first principles"

By homogeneity we mean a systematic review that is free of worrisome variations (heterogeneity) in the directions and degrees of results between individual studies. Not all systematic reviews with statistically significant heterogeneity need be statistically significant. As noted above, studies displaying worrisome heterogeneity should be tagged with a “*w*” at the end of their designated level.

Clinical Decision Rule. (These are algorithms or scoring systems that lead to a prognostic estimation or a diagnostic category.)
See note above for advice on how to understand, rate and use trials or other studies with wide confidence intervals.
Met when all patients died before the Rx became available, but some now survive on it; or when some patients died before the Rx became available, but none now die on it.
By poor quality cohort study we mean one that failed to clearly define comparison groups and/or failed to measure exposures and outcomes in the same (preferably blinded) objective way in both exposed and non-exposed individuals and/or failed to identify or appropriately control known confounders and/or failed to carry out a sufficiently long and complete follow-up of patients. By poor quality case-control study we mean one that failed to clearly define

§ Split-sample validation is achieved by collecting all the information in a single tranche, then artificially dividing this into "derivation" and "validation" samples.

Absolute sensitivity is a diagnostic test's sensitivity in a specific population. An absolute sensitivity of 100% means that all patients with the disease will test positive. A test with 100% absolute sensitivity has no false negatives.

Standard where the test is included in the reference, or where the testing affects the reference. It implies a level 4 study. Better-value treatments are clearly as good but cheaper, or better at the same or reduced cost. Worse-value treatments are as good and more expensive, or worse and the equally or more expensive. Validating studies test the quality of a specific diagnostic test, based on prior evidence. An exploratory study collects information and trawls the data (e.g. using regression analysis) to find which factors are 'significant'.

* By poor quality prognostic cohort study we mean one in which sampling was biased in favour of patients who already had the target outcome, or the measurement of outcomes was accomplished in <80% of study patients, or outcomes were determined in an unblinded, non-objective way, or there was no correction for confounding factors.

** Good follow-up in a differential diagnosis study is >80%, with adequate time for alternative diagnoses to emerge (for example 1-6 months acute, 1-5 years chronic)

“grades of Recommendation

- consistent level 1 studies
 - consistent level 2 or 3 studies or extrapolations from level 1 studies
 - level 4 studies or extrapolations from level 2 or 3 studies
 - level 5 evidence or troublingly inconsistent or inconclusive studies of any level

at least fair evidence that (the service) is ineffective or that harms outweigh benefits.

I.— The USPSTF concludes that the evidence is insufficient to recommend for or against routinely providing (the service). Evidence that (the service) is effective is lacking, of poor quality, or conflicting and the balance of benefits and harms cannot be determined.

NARRATIVE VERSUS SYSTEMATIC REVIEWS

Conventional reviews, so-called narrative reviews, are often subjective and may be biased because there are no explicit methods for searching the literature and reporting the findings (selection bias). Moreover, these reviews often lack a critical appraisal of the quality of the included studies. The absence of a standardized methodology makes it nearly impossible to replicate the results and conclusions made by a such traditional review which may introduce bias.

In an attempt to decrease bias and increase transparency, SRs use systematic methods to control bias and imprecision; use rigorous scientific methodology to search literature, to report and to critically appraise the underlying evidence. The transparency of the methods used for the EBM steps increase the likelihood that the results can be replicated by others.

HISTORY

While some find traces of SRs and EBM's origin in ancient Greece, others trace its roots to ancient Chinese medicine. Although testing medical interventions for efficacy has existed since the time of Avicenna's *The Canon of Medicine* in the 11th century, it was only in the last quarter of the 20th century that this effort evolved to impact almost all fields of health care and policy. Archie Cochrane's, a Scottish epidemiologist, advocacy for SRs caused increasing acceptance of the concepts behind evidence-based practice. Cochrane's work was honored through the naming of EBM research centers (*Cochrane Centers*) and an international organization, the Cochrane Collaboration. The explicit methodologies used to determine "best evidence" was largely established by the McMaster University research group led by David Sackett and Gordon Guyatt. The term "evidence based" was first used in 1990 by David Eddy⁸ and the term EBM first appeared in the medical literature in 1992 in a JAMA paper by Guyatt et al.⁹ The following years, the term EBM proved extraordinarily popular and the influence of EBM has been widely recognized both in lay publications (e.g., the *New York Times* listed EBM as one of its ideas of 2001) and academic press (e.g., the *BMJ* listed EBM as one of the 15 greatest medical milestones since 1840).

THE COCHRANE COLLABORATION

The Cochrane Collaboration is a group of over 10,000 volunteers in more than 90 countries who review the effects of health care interventions tested in randomized-controlled trials.¹⁰ A few reviews that are more recent have also studied the results of non-randomized, observational studies. The results of these systematic reviews are published as "Cochrane Reviews" in the Cochrane Library.

The Cochrane Collaboration was founded in 1993 under the leadership of Iain Chalmers. It was developed in response to Archie Cochrane's call for up-to-date, SRs of all relevant RCT of health care. Cochrane's suggestion that the methods used to prepare and maintain reviews of controlled trials in pregnancy and childbirth should be applied more widely was taken up by the Research and Development Program, initiated to support National Health Service in the United Kingdom. Funds were provided to establish a 'Cochrane Centre' to collaborate with others, in the UK and elsewhere, to facilitate systematic reviews of randomized-controlled trials across all areas of health care.¹¹

The goal of the collaboration is to help people make evidence-based decisions about health care by preparing, maintaining, and ensuring the accessibility of systematic reviews of the effects of health care interventions.

The systematic review of published research studies is a method used for evaluating particular treatments. The Cochrane Collaboration is one of the best-known, respected examples of SRs. A 2007 analysis of 1016 SRs from all 50 Cochrane Collaboration Review Groups found that 44% of the reviews concluded that the intervention was "likely to be beneficial", 7% concluded that the intervention was "likely to be harmful", and 49% concluded that evidence "did not support either benefit or harm". Almost all (96%) recommended further research.¹²

The Cochrane Skin Group (CSG) is a review group of the Cochrane Collaboration directed at dermatologic health care. The Cochrane Skin Group is a network of people from all over the world committed to producing and updating reviews of trials relating to skin conditions. The aim of the Cochrane Skin Group is simply to produce the best possible evidence on the effectiveness of health care interventions for people with skin problems.

The scope of the Skin Group is wide, and includes any skin problem that leads an individual to seek help from a health care provider. The Group also considers evidence about skin treatments that are sold over-the-counter or are widely available.

THE NEED FOR SYSTEMATIC REVIEWS

Physicians often base treatment decisions on a combined understanding of the pathogenesis of a disease, pharmacologic properties of possible drugs, known effectiveness, and logic. Although this paradigm seems appropriate, it

may be problematic, because its components may change over time resulting in different treatment regimens over time. The data on which treatment's effectiveness rely also varies from personal experience and empirical observations to large multicenter double blind RCTs. Keeping up with treatment innovations is now more challenging than ever because of the overwhelming information on clinical research. It is impossible, even for the most conscientious dermatologist to keep abreast of the 100 or so specialist dermatology journals.¹³ In 1995 already, it was estimated that healthcare professionals would need to read an average of 17–20 original articles daily to keep abreast of their field.¹⁴ It is unlikely that healthcare providers, consumers, researchers, and policy makers will have the time, skills and resources to find, appraise and interpret this amount of evidence and to incorporate it into healthcare decisions.

Systematic reviews (and EBM) respond to this challenge by identifying, appraising and synthesizing research-based evidence and presenting it as “the current state of clinical practice” in an accessible format.^{15,16} Also, SRs detect gaps of evidence. For example, the lack of RCT data of methotrexate in the treatment of psoriasis was identified in systematic reviews,^{17,18} and was subsequently assessed in a comparative RCT with cyclosporine in 2003.¹⁹ The importance of SRs is also illustrated by the observation that Cochrane SRs are highly cited in the literature. The impact factor of the Cochrane Database of Systematic reviews (CDSR), published within the Cochrane Library, and is growing. In 2007, the first impact factor was 4.654, then in 2008, 5.182 and in 2009, 5.653. So on average each Cochrane review is cited over five times by researchers around the globe within two years of publication.²⁰ On July 2 2010, the Lancet have announced that they will ask authors of all research reports submitted after August 1 2010 to put their work into the context of what has gone before, by either reporting their own, up-to-date systematic review or citing a recent systematic review done by others. This is important recognition of systematic reviews as a key element in understanding the findings from all new research.²¹

Additionally, in applications for research funds, SRs may be used to support the necessity of the research proposed and sometimes they are compulsory in research proposals. Furthermore, SRs are often used as a base for (inter)national guideline development and patient information leaflets.

Besides providing a nice summary of ‘all’ information available, SRs could also include some statistical methods for combining the results of individual studies (called meta-analyses).²² Pooling of data from a SR in a meta-analysis may increase the precision of the estimate (e.g., treatments’ efficacy) by increasing the study population, reduce biases and random error of individual studies and assess the heterogeneity between the available studies. Therefore, systematic reviews and meta-analysis may result in more reliable estimates than each individual study

separately (this is reflected in higher level of evidence in the grading system; see above).

WHAT IS A SYSTEMATIC REVIEW?

A systematic review attempts to collect all empirical evidence that fits pre-specified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.^{23,24} The key characteristics of a SR reflect the 5 steps of EBM.

Its goal is to minimize both bias (usually not only restricting itself to RCTs, but also seeking published and sometimes even unpublished reports, in every language) and random error (by amassing very large numbers of individuals).

Systematic reviews can cover a variety of domains, but the most commonly assessed domains are: (1) therapy and prevention (e.g., interventions for nail psoriasis), (2) diagnostic tests (e.g., the value of fluorescence to detect tinea capitis), and (3) others such as prognosis, etiology (causes of disease) and severe damage (e.g., the relationship between smoking and the occurrence of psoriasis). Until Issue 4, 2008, of the Cochrane Database of Systematic Reviews (CDSR), this database was only including SRs of therapeutic interventions and from thereon, it includes SR on diagnostic test accuracy as well.²⁵ Diagnostic test accuracy reviews are full-text systematic reviews of studies that assess the accuracy of a diagnostic test or tests for a given target condition in a specific patient/participant group and setting.²⁶

SRs on therapy should ideally be based on large, well designed RCTs because they provide the highest strength of evidence. If there are no such RCTs available, a SR may be based on studies with a lower level of evidence (see above), such as low quality RCT, nonrandomized studies or patient series at a cost that the SR’s conclusions are more likely to be biased. However, for many interventions there are no RCTs available or RCT investigations are not possible (e.g., in HIV research with clear data of retrospective analyses of the effect of certain anti-retroviral agents). SRs of observational studies are then appropriate. Cochrane reviews about the efficacy of interventions focus on only RCTs.

HOW AND WHERE TO FIND SRs?

Besides in PubMed and EMBASE, SRs can especially be found in the Cochrane Library, especially in the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (the DARE database), the Turning Research into Practice (TRIP) database and in SUMSearch. There is no Medical Subject Heading (MeSH) term for systematic review and also no publication type systematic review. However, these are available

for meta-analyse; “meta-analysis”[Publication Type] OR “meta-analysis as topic”[MeSH Terms]. The first one is a meta-analyse, the second one (MeSH) is concerning a meta-analyse.

In November 2001, a Systematic Reviews search filter was added to PubMed on the Clinical Queries screen to make it easier to retrieve citations for these distinctive articles.

See http://www.nlm.nih.gov/pubs/techbull/jf02/jf02_systematic_reviews.html

However, SR-filter finds more than SRs (e.g., guidelines) alone and it is and will be updated frequently. The SR-filter at this moment can be found at http://www.nlm.nih.gov/bsd/pubmed_subsets/sysreviews_strategy.html

THE SEVEN STEPS IN CONDUCTING A SYSTEMATIC REVIEW (CDSR)

A SR on therapy will be taken in the rest of this chapter as the base for describing the seven steps in conducting a SR. Prior to conducting a SR, a protocol has to be made. The protocol needs to describe the way the SR will be conducted. The 5 steps of EBM can be translated into 7 steps of SR describing the methodology of the SR.

Systematic reviewers may need to modify their original review protocol during its conduct, but changes should be reported and explained.

Step 1—The Aim of the SR

In this part, the background of the review will be discussed in the context of what is already known and the objective of the SR will be formulated in one or more clear clinical questions. The clinical questions can be translated into a PICO (Table 9-2). The ‘P’ stands for patient/population and may report on age, gender, disease and disease characteristics (e.g., adult patients with papulopustular rosacea) of the study population. The ‘I’ stands for intervention, which can be specified in for example administration mode, dose, frequency, duration (e.g., oral doxycycline, minocycline, and tetracycline). The ‘C’ stands for control/comparison

of the intervention studied (e.g., versus other active antibiotic treatments, versus placebo, versus topical agents). The ‘O’ of outcome, such as outcome parameters for efficacy (e.g., number of papels and pustels, Physician Global Assessment), or safety parameters (e.g., number of serious adverse events).

The objectives of the SR can be divided into primary objectives and secondary objectives. These should be clearly stated and the number of objectives should be restricted. The review’s primary objectives should normally reflect at least one potential benefit and at least one potential area of harm, and should be as few as possible. It is normally expected that the SR should be able to analyse these objectives if eligible studies are identified, and that the conclusions of the review will be based in large part on the effects of the interventions on these objectives.

Step 2—Search Methods

For the search of relevant studies often the ‘P’ and ‘I’ of the PICO will be used. If the focus is on specific controls or outcomes, this can be included as well. When looking for appropriate evidence the following databases can be searched.

Guidelines: National guidelines and guidance sites include among others the National Institute of Clinical Excellence (NICE), the Scottish Intercollegiate Guidelines Network (SIGN), British Association of Dermatology (BAD), The Dutch Society of Dermatology and Venereology (NVDV), National Guideline Clearinghouse. Guidance on many topics is also available at the Clinical Knowledge Summaries (formerly PRODIGY) website.

Systematic reviews, e.g. Cochrane Database of Systematic Reviews (Figure 9-1) and Database of Abstracts of Reviews of Effects (DARE database). The Cochrane Library is published on a monthly basis and made available both on CD-ROM and the Internet. In addition to Cochrane Reviews, The Cochrane Library provides other sources of reliable information: other SRs abstracts, technology assessments, economic evaluations, and individual clinical trials – all the current evidence in one single environment. DARE is the only database to contain abstracts of SRs that have been quality-assessed and is produced by the Centre for Reviews and Dissemination (CRD) at the University of York, UK. Each abstract includes a summary of the review together with a critical commentary about the overall quality. The database is a key resource for decision makers and can be used for answering questions about the effects of specific interventions, whether such questions arise from practice or in health care policy. DARE covers a broad range of health-related interventions and includes over 3,000 abstracts of reviews in fields as diverse as diagnostic tests, public health, health promotion, pharmacology, surgery, psychology and the organization and delivery of health care. DARE complements the Cochrane Database of Systematic Reviews by quality-assessing and summarizing reviews that have not yet been carried out by The Cochrane Collaboration.

TABLE 9-2—Explanation of the Acronym Pico in Defining the Aim of the SR

P	Patient population	Age, gender, disease characteristics
I	Intervention	Administration mode, dose, frequency, duration
C	Control/comparison	Placebo, active treatment or no treatment
O	Outcome	Outcome parameters for efficacy, health-related quality of life, adverse events, safety aspects, costs



FIGURE 9-1 Levels of Evidence. (Liberati A Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta/analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1/e34.)

Primary studies can be identified using PubMed, Medline, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), Bandolier and Lilacs.²⁷

CENTRAL includes details of published articles taken from bibliographic databases (notably MEDLINE and EMBASE), and other published and unpublished sources. CENTRAL records include the title of the article, information on where it was published (bibliographic details) and, in many cases, a summary of the article. They do not contain the full text of the article.

About three-fifths of the records in CENTRAL are taken from MEDLINE. In addition, each Cochrane Review Group maintains and updates a collection of controlled trials relevant to its own area of interest; these are called ‘Specialized Registers’.

Also, the Cochrane Skin Group has developed a specialized register of studies. A standard description of this register can be referred to and information should be included on when the specialized register was searched for the current version of the review and the search terms used should be listed.

As *grey literature* sources, internal reports, clinical trial registries and conference proceedings may be used. These sources of grey literature should be listed. Preferably, a list

of people (e.g., trial doctors or topic specialists) and organizations who were contacted for additional evidence. List any other sources used, which may include, for example, reference lists, the World Wide Web or personal collections of articles.

Clinical librarians are specialized in searching and may be very helpful to improve your search. In the method section of the SR, the methods used to identify studies should be summarized. The methods section should state the bibliographic databases searched, the dates and periods searched and any constraints such as language should be stated. Describe the search terms. The full search strategies for each database should be listed in an appendix to the review. Ideally, there are no language restrictions in order to minimize publication bias. International publications (English language) will overweight the evidence.

Present in a flow diagram the number of references found with the searches, the number of selected articles based on title and abstract, included based on full text, excluded and the reasons for exclusion see before. As studies with negative results of interventions (especially if industry sponsored) are less likely to be published than studies with positive results (i.e., publication bias),

perhaps not all the performed studies are published, so be aware of a (often) overestimation or underestimation of the effect.

Step 3—Criteria for Selection

Objective selection for studies to answer the question after extensive searching in several databases usually ends up with a large number of hits (e.g., 800–2,000 items). The eligibility criteria for excluding studies should be clearly stated. The selection based on these criteria should be done independently by two or more authors who agree on their decision. In case of disagreements, involvement of an additional author or by discussion may lead to consensus. After the search the first selection will be based on title or title and abstract. After this stage of crude selection, a finer selection will take place on the full text of the articles. Selecting the items should be taken on the basis of clear pre-established inclusion (e.g., papulopustular rosacea, RCTs, oral antibiotic treatments) and exclusion criteria (e.g., in vitro studies, animal studies, rosacea telangiectasia studies, case reports with less than 5 patients) based on the objective of the review and PICO.

The selection criteria are based on the following aspects:

Types of studies

Eligible study designs should be stated here, along with any thresholds for inclusion based on the conduct of the studies or their risk of bias. For example, ‘All randomized-controlled comparisons’ or ‘all RCTs with blind assessment of outcome’. Exclusion of particular types of randomized studies (for example, cross-over trials) should be justified.

Types of patients/participants/ Type of diseases

Patients groups, diseases, or conditions of interest should be described here, including any restrictions such as diagnostic subtypes, age groups and settings. Subgroup analyses should not be listed here.

Types of interventions

Experimental and comparator interventions should be defined here, under separate subheadings if appropriate. It should be made clear which comparisons are of interest. Restrictions on dose, frequency, intensity, or duration should be stated. Subgroup analyses should not be listed here.

Types of outcome measures

Specify here the efficacy and effectiveness outcomes, outcomes on adverse events or economic data. A subdivision of main outcomes and other outcomes is possible.

The main outcomes may be used in the ‘Summary of findings’ table. The timing of the outcome assessment may be used. Note that outcome measures do not always form part of the criteria for including studies in a review. If they do not, then this should be made clear. Outcome measures of interest should be listed in this section whether or not they form part of the eligibility criteria. It is important to address patient-reported outcomes.

Step 4—Critical Appraisal

Subsequently, the eligible articles have to be critically appraised for their methodologic quality. In accordance with the selection of the articles, this appraisal should preferably be done independently by two objective authors and disagreements have to be solved by discussion. The value or validity of the final recommendations in a SR depends strongly on the quality of the original articles. Many tool(s) are used to evaluate the methodologic quality of the studies such as Consolidated Standards of Reporting Trials (CONSORT statement) and the risk of bias table of the Cochrane. The use of a specific tool should be described or referenced. To appraise the methodologic quality of a study included in the review and thereby to detect various forms of bias, a series of validity items has to be scored for each article. Validity items include blinding for the allocation of intervention (solution: concealment of allocation), blinding of the outcome assessment (solution: blinding of outcome assessment) and completeness follow-up (solution: no selective failure).

For the Cochrane SRs, the risk of bias table is introduced as a tool for assessing the validity of the individual studies.

In case of bias, the effect of bias on the results of the study should be analyzed.

Step 5—Objective Data Collection

The methods for data collection should be described. Preferably, a data collection form is used and data are extracted independently by more than one author, because the difference in reading and interpreting the data from the studies can occur. If relevant, methods for processing data in preparation for analysis should be described.

Data extracted for methodologic quality and outcomes could be presented in so-called evidence tables. It contains aspects of the reference, the methodologic quality (methods of blinding, concealment of allocation, intention to treat analyses, level of evidence) (Table 9-3), study characteristics (endpoints, duration of follow-up), patients characteristics (gender, type of disease, severity, duration), treatment characteristics (the intervention(-s), treatment frequency, duration, dose, setting), the outcome parameters (number of adverse events, the number of serious adverse events [SAE] and the number of dropouts

TABLE 9-3—Risk of Bias of Included RCT

	Adequate randomisation?	Adequate concealment of allocation?	Adequate blinding?	Incomplete data reported?	Free of selected reporting?	Free of other bias?
Author et al.	Yes	Unclear	Participants no	No	Unclear	Unclear
Year of publication	Yes		Researchers no Outcome assessment no			

because of AE) and results (impact, efficacy, safety, cost (Table 9-4). Additionally, the source of funding may be reported.

Step 6—Analysis (If Possible Meta-Analysis)

The results of the reviewed studies will be scrutinized and examined to what extent these results can be merged. Either a descriptive summary will be given or, when it is possible to combine the results numerically (statistical pooling), a meta-analysis will be performed. The effect measures of choice should be stated. For example, odds ratio (OR), risk ratio (RR) or risk difference (RD) for dichotomous data; mean difference (MD) or standardized mean difference (SMD) for continuous data.

Meta-analyses

As mentioned before in this chapter, pooling of data from a SR in a meta-analysis may increase the precision of the estimate (e.g., treatments' efficacy) by increasing the study population, reduce biases and random error of individual studies and assess the heterogeneity between the available studies. Thus in addition to a qualitative summary, a quantitative summary (statistical pooling or meta-analysis) may be a part of a SR. By combining data from several studies, the possibility of a more accurate estimate of the effect increases and subgroup analyses may be carried out.

Not always, is it possible or desirable to combine data in meta-analyses. It became clear about meta-analyses that there could be serious methodologic limitations because the pooled results may give an apparent accuracy. There is need for a certain clinical, methodologic, and statistical homogeneity between the studies. Performing and interpreting meta-analysis can be potentially misleading if the included studies are clinically or statistically heterogeneous. Studies that are included in meta-analysis may differ (i.e., show heterogeneity) in several ways: (1) heterogeneity of inclusion/exclusion criteria (demography/past medical histories/present illnesses of patients, method of disease diagnosis, duration/severity of the disease, etc), (2) heterogeneity of therapies (Different drugs from one class such as topical corticosteroids), different treatment durations, different routes of administration, different comparators compared to the targeted drug. (3) heterogeneity of pooled outcome measures, (4) Mixing high and low quality RCTs ** (low sample size, pseudorandomized/nonrandomized, non-blind, lack of follow-up, incomparable baseline data, in some studies), (5) Heterogeneity of effect size in included studies (some studies show pretty big effect size of efficacy/safety, some show no difference with placebo). Therefore, the eligibility criteria should be clearly stated and should try to minimize heterogeneity as much as possible. If heterogeneity of studies is present, the results of the analysis should be interpreted with great caution and it should be considered that a meta-analysis is inappropriate.

TABLE 9-4—Evidence Table: Results

	Efficacy/effectiveness	Time to response (weeks)	Duration of remission (months)	Concomitant medication	AE's (n of events)	SAE's (n of events)
Author et al.	% Complete remission active treatment ($p<0.05$)	e.g. 8 weeks	e.g.18	e.g. Prednisolone 10–60 mg (all)	e.g.Gastrointestinal complaints (1)	e.g. Septic arthritis (1), epidural abscess (1)
Year of publication	% Complete remission in conventional group ($p>0.05$)					

AE, adverse event; SAE, serious adverse event.

Statistically, a meta-analysis calculates a weighted average of all effects. The weight given to the results of an individual study depend on the size of the study's populations. It is intuitively logical that larger studies with more "events" give more weight: larger studies provide more stable estimates than small studies. An investigation of two times in 1000 patients carries more weight than a study of 100 patients two times. Suppose the first study resulted in a relative risk (RR) of 10 and the second, smaller study in one of RR 2, and then the pooled RR come closer to 10 than to 2. The larger the size of the study and the more patients with the studied outcome, the greater the weight of research in a meta-analysis.

In the graphical representation of a meta-analysis (also called 'forest' plot), several characteristics of each study are presented such as its first author, year of publication, the number of patients, and the effect size (e.g., RR or OR), and its 95% confidence interval (95% CI). The blue square, the diamond, represents the "point estimates" of the effect size and its size often reflects the sample size and the horizontal lines reflect the 95% CI (which is often narrower for larger studies). The meta-analysis of a favorable outcome ("rehabilitation", "cure", "and improved") with an effective intervention will be graphically a diamond right of the neutral line (and the RR is greater than 1). The meta-analyses of an unfavorable outcome ("deceased", "myocardial infarction", "worse") and the protective effect of an intervention is reflected by the fact that the diamond is located left of the neutral line (and then the RR is less than 1). The vertical line gives the "value neutrality" of the risk estimate (for RR it is 1 and for OR 0) where there is no difference in effect. Below the forest plot figure, results of statistical tests are given. To pool data, program Review Manager 5 (free to download from the web)

Unit of analysis issues

Special issues in the analysis of studies with nonstandard designs, such as crossover trials, studies with multiple treatment groups and cluster-randomized trials, should be described. Alternatively, optional headings specific to the types of studies may be used.

Dealing with missing data

Strategies for dealing with missing data should be described. In most cases it concerns participants lost to follow (i.e., drop-outs) who were excluded from the presented analysis in a per-protocol analysis. For an intention-to-treat analysis, the (descriptive) statistics of the primary outcome have to be re-calculated. Ideally, the original data are acquired from the responsible researchers.

Assessment of heterogeneity

Approaches to addressing clinical heterogeneity should

be described, along with how the authors will determine whether a meta-analysis is considered appropriate. Methods for identifying statistical heterogeneity should be stated (e.g., visually, using I^2 , using a chi-squared test). Clinical homogeneity will be received if the studies that are included in the SR are sufficiently similar with respect to persons under investigation, the comparison, intervention (dose, duration of treatment, allowance of co-medication) and outcomes (outcome parameters, versions of the same outcome measure, tools to measure the effect). For clinical heterogeneity, there are no proper criteria available and depends on expertise.

Moreover, methodologic homogeneity is important. In- and exclusions criteria may incorporate aspects of the clinical and methodologic quality to homogenize the ingredients of the SR and meta-analyses.

If the results of different studies, despite the adoption of clinical and methodologic homogeneity differ, we speak of statistical heterogeneity. This may be due to coincidence and actual differences in clinical or methodologic quality. The assessment of statistical heterogeneity is difficult. Visual inspection of the degree of overlap in confidence intervals is a method to examine heterogeneity. The intervals overlap "enough" then there is no heterogeneity and the investigations can be pooled.

Assessment of reporting biases

This section should describe how publication bias and other reporting biases are addressed (for example, funnel plots, statistical tests, and imputation). However, authors should remember that asymmetric funnel plots are not necessarily caused by publication bias (and that publication bias does not necessarily cause asymmetry in a funnel plot).

Data synthesis

The choice of meta-analysis method should be stated, including whether a fixed-effect or a random-effects model is used. If meta-analyses are not undertaken, systematic approaches to synthesizing the findings of multiple studies should be described. All planned subgroup analyses should be listed (or independent variables for meta-regression).

Step 7—Conclusions and Recommendations

After the analysis, conclusions should be drawn to the initial clinical question (the PICO of the SR). In addition to providing a summary of the evidence, SR reflect to what extent a clinical question has been studied, the quality of the available studies and whether it confirms the original hypothesis (e.g., is a treatment effect positive, negative or neutral). A general interpretation of the results in the context of other evidence should be given. Although the primary goal of a SR is not to formulate recommendations, the findings of the SRs or meta-analyses are often the base on which recommendations are formulated in guidelines,

which may invite some subjective input on behalf of the authors and involved experts. If gaps of evidence are found, recommendations for further research should be listed.

In this step, the limitations of the SR may be discussed. The effect of different forms of bias, if applicable, should be explained. In this perspective, the funding sources for the systematic review should be described, as well as the role of funders for the SR.

CHECKLISTS OF SYSTEMATIC REVIEWS

The value of a SR depends on what was done, what was found, and the clarity of reporting. The reporting quality of SRs varies and therefore limits the ability for readers to assess the strengths and weaknesses of those reviews.^{28,29} In 1996, an international group developed a guidance called the QUOROM statement (Quality of Reporting Of Meta-analyses) which focused on the reporting of meta-analyses of RCTs.³⁰

PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) is a revision of this guideline, which have been updated to address several conceptual and practical advances in the science of SRs. The aim is to help authors to improve the reporting of SRs and meta-analyses. PRISMA is focussed on RCTs but can be used for other study types, particularly evaluations of interventions. It may be helpful for critical appraisal of published SRs.

PRISMA (www.prisma-statement.org) uses the current terminology used to describe SRs and meta-analyses and both SRs and meta-analyses are included. The conceptual issues in the evolution from QUOROM to PRISMA includes that completing a SR is an iterative process, the protocol should be publicly accessible to judge between appropriate and inappropriate modifications. Reviewers may need to modify their original protocol during its conduct. SRs should report the assessment of the risk of bias in the included studies. For studies included in a SR, a study level assessment (e.g., adequacy of allocation concealment) and for some features, an outcome level assessment are needed. An outcome level assessment involves evaluating the reliability and validity of the data for each important outcome by determining the methods used to assess them in each individual study.³¹ The quality of evidence may differ across outcomes, even within a study. The primary efficacy outcome may be carefully and systematically measured whether the assessment of harms rely on spontaneous reports by investigators. When this information is reported it allows an assessment to which the extent to which an estimate of effect is correct is. The PRISMA statement consists of 27 items and a 4-phase flow diagram. PRISMA is a living document. Readers are invited to comment on the revised version, through the PRISMA website.

AMSTAR

The objective of AMSTAR (Assessment of Multiple SysTemAtic Reviews) was to develop an instrument to

assess the methodologic quality of SRs, building upon previous tools, empirical evidence and expert consensus. The tool consists of 11 items and has good face and content validity for measuring the methodologic quality of systematic reviews. The authors conclude that additional studies are needed with a focus on the reproducibility and construct validity of AMSTAR, before strong recommendations can be made on its use.³²

COSMIN

The COSMIN (COnsenses-based Standards for the selection of health status Measurement Instruments) checklist is an instrument to assess the risk of bias in studies on clinometric properties, as a first step to improve the methodologic quality of SRs on clinometric properties. It was developed in an international Delphi study to evaluate the methodologic quality of studies measurement properties of health-related patient reported outcomes (HR-PROs).

For the measurement of health-related patient-reported outcomes, it is important to evaluate the methodologic quality of studies in which the measurement properties of these instruments are assessed. In methodologic good studies on measurement properties, the conclusions are more trust-worthy.³³

Limitations

Since SRs summarize large amounts of information there may be loss of information of individual studies.^{1,34} The search for evidence is stopped at a certain point in time and the final publication of the SR may take an additional year, therefore, SR may not include all the evidence at time of publication. This issue is particular important in treatments of diseases that are evolving quickly such as psoriasis. Updating SRs is a pivotal part of initiating, but also maintaining, a (Cochrane) SR.¹⁰ The content of a SR depends on the evidence found, of which the majority derives from published data in international journals. Therefore, treatments studied more rigorously in multiple RCTs are more likely to achieve the highest level of evidence (see later). Relatively new patented drugs are much more likely to be studied in large, high quality RCTs because of industry funding, which is in contrast to older drugs that ran out of patent.³⁵ For example, the level of evidence for methotrexate or fumaric acids in the treatment of psoriasis is fairly low compared to that of treatments that are on the market for less than 5 years. Moreover, studies yielding positive and significant results of a treatment are more likely to be published (i.e., publication bias) and therefore are overrepresented in SRs.³⁴ Ideally and in addition to published data, an attempt should be made to include nonpublished data from pharmaceutical companies and the abstracts of meetings. The degree of publication bias can also be estimated statistically.³⁶ This illustrates the importance of registration of clinical trials

in online freely accessible databases (e.g., www.clinicaltrial.gov). However, this system is not completely waterproof as recently demonstrated in a study on registered and published outcomes.³⁷ If language restrictions are applied (often with a focus on English publications), there is often an overestimation of the effect because positive findings are more likely published in international peer reviewed journals than studies with negative results. In the current categorization of level of evidence, RCTs are overemphasized: small, low quality RCTs rank higher than well-performed observational studies.³⁸ There is a trend to upgrade well-performed observational studies. One of the major advantages of this study types is that it assesses the effect of treatments (e.g., effectiveness, safety, preference, and costs) in real life situations. Patients included in RCTs reflect a healthy and well-defined subgroup of the entire patient population that a physician may encounter during daily practice.³⁹ In practice, many patients are much more complicated because they may be older or younger, may have important past or current medical problems, use other drugs, may have other disease subtypes, and be less compliant. Moreover, RCTs often do not last longer than 24 weeks and several therapies may lose some of its effectiveness over time, and its dosage has to be increased, has to be discontinued and/or combined with other drugs.

To adequately summarize different datasets, uniform outcome parameters are warranted (especially in meta-analysis) implying that studies using other endpoints may not fully weigh on the final result. For example, in contrast to the PASI75 in psoriasis, there is a wide variety of outcomes used in atopic dermatitis studies, which makes it difficult to compare and pool data from the different studies. To conclude, many more limitation could be listed here but the authors believe that to the best of our abilities, systematically summarising evidence is nowadays impossible to ignore in our work and very necessary.

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Treatment of Hand Dermatitis

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INTRODUCTION

Hand dermatitis (also known as hand eczema) is a relapsing-and-remitting disease that is common and frequently chronic. Our hands are important tools of communication and function, thus the location of this dermatitis and the pain and irritation associated with hand dermatitis affects patients' ability to perform daily tasks both at home and in the workplace. The visibility of the dermatitis is a source of embarrassment and psychologic stress for many patients impacted by this disease.¹

EPIDEMIOLOGY AND ETIOLOGY

Hand dermatitis is a very common disorder of the skin, affecting all age groups,² with a prevalence in the general population of roughly 10%³ and incidence of 7.7-9.9% cases per 1000 person-years.⁴ In certain occupational settings, prevalence may be increased to 30% or more, often making hand dermatitis the most common occupational skin disease.^{5,6} People particularly at risk are those who participate in "wet-work," such as construction workers,⁶ hairdressers,⁷ housekeeping personnel,⁸ hospital employees,⁹ gardeners,¹⁰ and metalworkers.¹¹ Some studies have documented a higher prevalence of hand dermatitis in women than men, attributed to women's increased exposure to 'wet work' because of their disproportionately greater role in household chores.¹²

The etiology of hand dermatitis is multifactorial, but disruption of the normal skin barrier is thought to be a key factor in its pathogenesis. Subtypes of hand dermatitis attempt to classify the disease based on both etiologic and morphologic characteristics. Currently, there is no universally accepted classification system available for hand dermatitis.¹³ Generally accepted sub-classifications, as documented by Warshaw et al.¹⁴ are: contact dermatitis (irritant or allergic), atopic hand dermatitis, recurrent vesicular hand dermatitis/pompholyx (also known as dyshidrotic eczema), hyperkeratotic hand dermatitis (also known as tylotis eczema), nummular (discoid) hand dermatitis, and chronic vesicular hand dermatitis.

Irritant contact dermatitis is the most frequent diagnosis, comprising 35% of patients in the general population with hand dermatitis. This is followed by atopic dermatitis

(22%) and allergic contact dermatitis (19%).¹² Recurrent vesicular hand dermatitis and hyperkeratotic hand dermatitis account for 5-20% and 2% of all hand dermatitis cases, respectively.^{15,16} In the occupational setting, irritant contact dermatitis may account for up to 76% of cases of hand dermatitis.¹⁷ In practice, it is not uncommon for a mixture of hand dermatitis subtypes to coexist.^{18,19}

Exogenous Etiology

Contact dermatitis is a cutaneous reaction to exogenous (external) factors within the environment.² Since our hands are so intimately involved with our environment, they are particularly predisposed to the development of contact dermatitis. There are two types of contact dermatitis: irritant contact dermatitis and allergic contact dermatitis.

Irritant contact dermatitis (ICD) is a reaction to direct damage of keratinocytes that results from contact with harmful chemicals or physical agents (irritants). This damage is not immune mediated, but is the result of the irritant itself.² Damage and the resulting dermatitis may be acute or chronic in type. Acute irritants, such as chemical acids and bases, will cause inflammation in anyone who is in contact with them. Chronic ICD is more common and results from the repetitive use of mild skin irritants, such as soap and water, which have a cumulative effect on the skin over time.¹⁵

Frictional irritants, such as repeated exposure to trauma, rubbing, vibration, or pressure, have also been reported to cause a form of contact dermatitis.²⁰ Chronically, frictional dermatitis has been implicated in the development of hyperkeratotic hand dermatitis.^{16,20}

Allergic Contact Dermatitis (ACD) is a cutaneous immune-mediated reaction that results from contact with a specific allergen to which a patient has developed sensitivity.²¹ It is a type IV, T-cell mediated, delayed hypersensitivity reaction. Lesions often appear more acutely than in ICD, generally occurring within 48 hours of reexposure to the allergen.¹⁵ ICD and atopic dermatitis may also predispose a patient to ACD because in both, the epidermal barrier function is disrupted allowing greater penetration of allergens.¹⁴

Endogenous Etiology

Atopic dermatitis (AD) is an inherited endogenous dermatitis. Although a maternal history of atopy is a strong predictor for the development of AD, interplay between genes and the environment most likely leads to development of the disease.²¹ One hypothesis suggests that atopic individuals have a genetic alteration in the integrity of their skin barrier, which leads to a potent Th2 allergic response when the skin is presented with antigen. This then leads to an increased production of IL-4 and IgE.²² Atopic hand dermatitis has also been associated with a mutation in the gene coding for filaggrin, a protein involved with skin barrier protection.²³ The loss of skin barrier integrity can predispose atopic individuals to contact dermatitis by allowing increased skin penetration of irritants.²⁴ One-third to one-half of patients presenting with hand dermatitis was found to be atopic, and atopic patients are at a 13.5-times greater risk of developing occupational dermatoses than nonatopic patients.^{24,25}

Exogenous or Endogenous Etiologies?

Acute or recurrent vesicular hand dermatitis (RVHD) is traditionally classified as an endogenous dermatitis, although there is increasing evidence that recurrent vesicular hand dermatitis is in many cases a cutaneous reaction to exogenous contact allergens: metal allergy (most notably to nickel, chromate, and cobalt), cosmetic and hygiene product sensitivity (especially shower gel), tobacco smoking, hyperhidrosis, history significant for atopy, and psychologic stressors have all been associated with the condition.^{26,27} Chronic vesicular hand dermatitis (CVHD) may be a chronic form of RVHD, although it may also result from other types of hand dermatitis.²⁸ RVHD may also be confused with a dermatophytid ('id') reaction—the formation of vesicles on the fingers in response to a distal infection—most commonly tinea pedis.^{27,28}

Both hyperkeratotic hand dermatitis and nummular hand dermatitis have unknown etiologies,^{25,29} although hyperkeratotic hand dermatitis has been associated with chronic exposure to friction.^{16,20}

CLINICAL MANIFESTATION

Hand dermatitis is not a uniform disease. Its morphology varies based on its etiology, chronicity, and severity. Common clinical manifestations include: erythema, edema, papules, vesicles, scaling, hyperkeratosis, dryness, lichenification, and fissuring that may involve a few fingers to the whole hand surface.³⁰ The subtypes of hand dermatitis frequently have morphologic and distributional patterns that may suggest causation, but this is rarely exact, and frequently, there is a mixture of subtypes present.^{12,30}



FIGURE 10-1 'Apron-like' pattern of irritant contact dermatitis.

Contact Dermatitis

In general, acute contact dermatitis is characterized by erythema, papules, vesicles or bullae, urticaria, excoriations, and crusts, while chronic contact dermatitis is characterized by dryness, scaling, lichenification, and fissuring that can result immediately or days after exposure to the irritant/allergen.¹⁸ Both forms can have associated pruritus and/or pain.¹⁸ Specific features of ICD and ACD are listed below:

Irritant Contact Dermatitis

ICD is commonly associated with wet work. It generally involves the finger web-spaces and may extend to the dorsal and/or ventral surfaces of the hand in an "apron-like" pattern (Figure 10-1).¹⁴

Allergic Contact Dermatitis

ACD is generally indistinguishable from ICD, but it favors the fingertips, nailfolds, and dorsal aspects of the hands—generally sparing the palms (Figure 10-2).²⁵ In fact, a dermatitis that spreads to the dorsal aspects of the hands is said to be characteristic for ACD.³¹ Edema and vesicles



FIGURE 10-2 Acute allergic contact dermatitis.

are common features.²¹ ACD lesions generally begin within 48 hours of allergen exposure and are well demarcated.¹⁵

Occasionally, ACD may be confused with the less common, contact urticaria. Contact urticaria is a form of type I, IgE mediated, hypersensitivity reaction, usually in response to natural rubber latex, although certain foods and ammonium persulphate, which is used in hairdressing bleach, have also been implicated.³² It is characterized by wheals that develop 30 minutes after contacting the allergic substance and usually resolve within 24 hours. 87% of patients with contact urticaria have predominant hand involvement.³² If contact urticaria is suspected, radioallergosorbent skin tests and skin prick testing to natural rubber latex and the patients own food samples should be performed.^{18,32}

Atopic Dermatitis

Atopic dermatitis lesions are eczematous and constantly pruritic.²¹ Acutely, the lesions are papulovesicular with associated pruritus, weeping, and scaling. Excoriations and crusting are common. Chronically, xerosis and lichenification predominate.²¹ Atopic dermatitis is associated with atopy, generally defined as a triad of allergic rhinitis, eczema, and asthma.¹³ Lesions typically begin in infancy and have different locations and morphologic features in infants, children, and adults. Infants typically have ill-defined, erythematous lesions with associated scaling and crusting located on the face, scalp, and extensor surfaces of the legs, often sparing the diaper area; lichenification is not present. Children have eczematous and exudative lesions most often in the flexural creases; lichenification, xerosis, excoriations, and crusting may be present (Figure 10-3). Adults generally have a regression of their lesions, but lichenification and xerosis persist.²¹ Up to 70% of patients with atopic dermatitis have hand involvement, most commonly on the dorsal aspect of the hands.¹⁵ Extension onto the volar wrist is classic for this subtype.^{15,31}

Acute or Recurrent Vesicular Hand Dermatitis/Pompholyx (also known as Dyshidrotic Eczema)

There is much confusion and controversy surrounding the terminology regarding acute or recurrent vesicular hand dermatitis.^{28,33} Originally, the presentation of recurrent crops of vesicles on the lateral aspects of the fingers and palms was referred to as '*dyshidrosis*' because it was believed that the etiology originated from a disorder of sweat glands;³³ however, that theory has been disproved.²⁶ Later, the term *pompholyx* (derived from the Greek *cheir*-*pompholyx* meaning "hand and bubble") was suggested to describe this vesicular eruption on the hands and feet.^{15,33} Although strict criteria have been suggested as to how these two definitions are to be used, these criteria are rarely adhered to.³³ Therefore, recently, authors have proposed



FIGURE 10-3 Atopic hand dermatitis, with prominent lichenification, in a 3-year-old Somali girl.

the use of "*acute and recurrent vesicular hand dermatitis*" to replace the terms *dyshidrosis* and *pompholyx*.^{28,33}

This text, in keeping with the classifications described by Warshaw et al.¹⁴ differentiates acute or recurrent vesicular hand dermatitis (RVHD) from chronic vesicular hand dermatitis (CVHD). Recurrent vesicular hand dermatitis (RVHD) is defined as a relapsing dermatitis in which recurrent, intensely pruritic crops of clear sterile vesicles or bullae, without surrounding erythema, appear on the sides of the fingers, palms, or plantar surface of the feet (Figure 10-4).³³ The absence of erythema associated with vesicles helps differentiate this diagnosis from ICD or ACD.³³ Hands are more commonly involved than the feet (80% and 12% of cases, respectively).²⁷ An acute attack usually begins with burning and itching, followed by deeply-seated vesicles that appear within 12-24 hours. These vesicles may persist for a period of 2 to 3 weeks and then resolve with associated desquamation.²⁶ They generally recur at unpredictable intervals.³³ Rarely, severe, noninflamed, symmetric, bullous eruptions may be present on the palmar or plantar surfaces; the term pompholyx is classically used to describe this more dramatic presentation.^{28,31} When the distal phalanx is involved, an attack of RVHD can cause a transverse ridge in the nail. Assessing the number of ridges can clue the practitioner into the number and frequency of RVHD attacks.²⁶



FIGURE 10-4 Vesicular hand dermatitis of the palm.

Chronic Vesicular Hand Dermatitis

The lesions of chronic vesicular hand dermatitis (CVHD) are constant (unlike RVHD which wax and wane), pruritic, vesicular, and mostly palmar, frequently stopping at the wrist and sparing the dorsal hand or involving only the fingertips.³⁴ Additionally, vesicles of CVHD have an erythematous base, unlike those in RVHD.^{33,34}

Hyperkeratotic Dermatitis

Hyperkeratotic hand dermatitis is characterized by symmetric circumscribed areas of dense, dry, scaly, hyperkeratotic skin, often with painful fissures, located on the proximal or middle of the palms; vesicles or pustular lesions are generally absent (Figure 10-5).^{25,29} It occurs commonly in men aged 40 to 60, who have a history of manual labor, although



FIGURE 10-5 Hyperkeratotic hand dermatitis with fissures in a middle aged female.



FIGURE 10-6 Nummular hand dermatitis.

it is also present in women.²⁹ Hyperkeratotic hand dermatitis generally has a constant chronic course.²⁹

Nummular (Discoid) Hand Dermatitis

The clinical manifestations of nummular hand dermatitis are round or oval (“coin-shaped”) eczematous plaques on an erythematous base that begin as grouped papules or papulovesicles that then coalesce into plaques, often with areas of central clearing.^{35,36} The lesions have an asymmetric distribution on the hands, distinct border, some scaling, and are intensely pruritic (Figure 10-6).^{35,36} Lesions are more common on the extremities during the winter months, favoring the dorsum of the hand and distal fingers.^{14,31} Chronic nummular dermatitis lesions are often difficult to treat and recur at the same sites.^{35,36}

DIAGNOSIS

Although distribution on the hand and physical characteristics may hint to a diagnosis, it is often difficult to translate the morphologic characteristics of hand dermatitis into a definite subtype classification. Additionally, there are no standardized diagnostic criteria for diagnosing hand dermatitis. Therefore, a thorough history, diagnostic examination, and work-up, including patch testing, are needed.¹⁹ Dermatoses of hand, such as tinea mannum, photosensitivity reactions, and infections should be excluded. Diagnostic questioning should evaluate the pathogenesis of the lesions (Figure 10-7), and physical examination should localize the lesions and describe their morphology.²

There is no diagnostic test available for ICD; it is a diagnosis of exclusion after ACD and AD have been ruled out.¹⁵ Almost any of the 85,000 known chemicals in the world environment can be irritative if given the right circumstances, however there are only about 3,000 substances identified as contact allergens.^{2,21} Patch testing for these allergens is the gold standard for diagnosing ACD and an essential part of the diagnostic work-up for hand dermatitis.¹⁸

<ul style="list-style-type: none"> • History of any medical problems, especially atopic dermatitis • Any previous episodes of hand dermatitis • Onset, location, and progression of current symptoms • Description of morphology • History of remissions • Exacerbating and relieving factors • Related non-cutaneous symptoms 	<ul style="list-style-type: none"> • Work history • Hobbies • Exposure to animals or fur • Household activities and cleaning products • Personal care products used • Treatments tried and/or medications taken or applied to the affected areas • Any friends, family, or co-workers similarly affected • Family history of atopy or skin disease
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Adapted from Drake et al.² and Diepgen et al.¹³

FIGURE 10-7 Pertinent history questions*.

As described by Bourke et al.¹⁸ patch testing involves the application of allergens to the skin at standardized concentrations via standardized vehicles. Allergens are placed in an area free of dermatitis, and attempts should be made to control dermatitis elsewhere on the body. The back is commonly used for convenience. Allergens are placed on Day 1, then kept under occlusion and assessed between Day 3 and 5. Later additional readings may reveal more positives.¹⁸ Standard screening series are used as ‘baseline’; in addition to the screening series, additional patch tests should be performed with the patient’s own materials and personal products. Once a positive allergen is identified through patch testing, it must be determined whether this substance is clinically relevant. Textbooks on contact dermatitis may help in this endeavor.¹⁸

Patch testing is also helpful in confirming suspected recurrent vesicular hand dermatitis (RVHD). Although this diagnosis is generally made clinically, patch testing can not only exclude ACD, but may also reveal sensitivities to certain agents which predispose the patient to RVHD eruptions.²⁶ If a patient has sensitivity to nickel, cobalt, or chromate, an oral challenge with these substances may reproduce the vesicular flare,²⁸ although this theory is controversial.³³ When diagnosing RVHD, it is important to exclude a dermatophytid ‘id’ reaction by assessing for fungal infection of the feet and intertriginous areas through skin scrapings and cultures.²⁸

Atopic dermatitis can be diagnosed in a patient with a history of itchy skin who has three or more of the following: (1) a history of rash in the skin creases, (2) a history of generally dry skin within the last year, (3) a personal history of asthma or hay fever, (4) onset under the age of 2, and (5) visible flexural dermatitis.³⁷ These five criteria were found to diagnose atopic dermatitis with a sensitivity and specificity of 80 and 97%, respectively.³⁷

Hyperkeratotic hand dermatitis, nummular hand dermatitis, and chronic vesicular hand dermatitis are all diagnosed based on their clinical morphology.^{14,29,34,36}

It is important to not delay when making a diagnosis of hand dermatitis because if the diagnosis is postponed for

more than twelve months, there is an increased likelihood that the dermatitis will become chronic.³⁸ Currently, 5-7% of patients with hand dermatitis are classified with chronic or severe symptoms, and of these, 2-4% are resistant to traditional topical treatments.²⁵

TREATMENT

The goal of treatment is to reduce clinical symptoms, improve the patient’s quality of life, and minimize relapses.

While acute flares of hand dermatitis can often be managed with avoidance of the inciting agents and topical corticosteroids, as hand dermatitis becomes chronic, it becomes more difficult to treat, even though many treatment options are available.^{30,38} Despite the high prevalence of hand dermatitis in the population and great burden the disease has on both the individual and society, few well-designed randomized controlled trials that have been performed to guide clinical practice. In fact, van Coevorden et al.³⁹ attempted to assess the quality of studies pertaining to treatment of hand dermatitis and determined that the studies were of such poor quality that their overall recommendation was to have researchers “start again”. Thus, the treatment of chronic hand dermatitis is rarely evidence based.

Lifestyle changes

Lifestyle changes are the foundation of treatment for hand dermatitis and can be summarized as: prevention, avoidance, protection, and substitution.

Although it is impossible to predict who will develop hand dermatitis, certain people have an increased tendency to develop the disease: Atopics, women, and people in ‘wet-work’ occupations are all at increased risk.^{12,24,25} Preventing hand dermatitis through education regarding lifestyle modification practices (Figure 10-8), workplace evaluations, and the prescreening of workers for atopy or allergen sensitivity in high risk occupations can help minimize development of the disease.^{40,41}

Avoidance is the hallmark of both ICD and ACD, where identified irritants and/or allergens are directly involved in the dermatitis. Complete avoidance of triggers is ideal but not always possible; as such, certain individuals may need to change jobs in order to control their dermatitis.²⁵ Additionally, avoidance of exacerbating factors, such as water (‘wet-work’), sweating, humidity, dryness, friction, cold, or heat as it pertains to the patient, can help control symptoms.⁴²

In the case where an irritant/allergen cannot be easily avoided, or when performing ‘wet work’, protection of the hands is necessary. For household work polyvinyl chloride (PVC) gloves are recommended.¹⁴ These should either have a cotton liner or be worn over cotton gloves to maximize protection because the gloves themselves

Hand washing and moisturizing

- Use lukewarm or cool water and mild cleansers without perfume, coloring, or antibacterial agents and with minimal preservatives. In general, bar soaps tend to have fewer preservatives than liquid soaps (Cetaphil or Aquanil liquid cleansers or generic equivalents are exceptions).
- Pat hands dry, especially between fingers.
- Immediately following partial drying of hands (e.g., within 3 minutes), apply a generous amount of a heavy cream or ointment (not lotion); petroleum jelly, a one-ingredient lubricant, works well.
- It is helpful to have containers of creams or ointments next to every sink in your home, as well as next to the bed, next to the TV, in the car, and in multiple places at work.
- Moisturizing should be repeated as often as possible throughout the day, ideally, 15 times per day.
- Avoid rubbing and scrubbing, the use of washcloths, and the overuse of soap or water.

Occlusive therapy at night for intensive therapy

- Apply a generous amount of your doctor's recommended emollient or prescribed medicine to your hands, then, put on cotton gloves, and wear overnight.

When performing 'wet-work'

- wear cotton gloves under vinyl or other nonlatex gloves;
- try not to use hot water, and decrease the exposure to water to less than 15 minutes at a time if possible;
- if possible, use running water rather than immersing hands; and
- remove rings before work (wet or dry).

Wear protective gloves in cold weather and for dusty work.* For frictional exposures, wear tight-fitting leather gloves (e.g., baseball, riding, or golfing gloves).

Avoid contact to the following, if possible:

Shampoos
 Fruits and vegetables' peelings, especially those from citrus fruits
 Polishes of all kinds
 Solvents (e.g., white spirit, thinners, turpentine)
 Hair lotions, creams, and dyes
 Detergents and strong cleansing agents
 Fragranced chemicals
 "Unknown" chemicals

* Heavy-duty vinyl gloves are better than rubber, nitrile, or other synthetic gloves because vinyl is less likely to cause allergic reactions.

FIGURE 10-8 Sample handout on lifestyle management for patients with hand dermatitis. (Reprinted with permission from Warshaw, et al.¹⁴)

may exacerbate the dermatitis.¹⁵ Gloves may need to be removed frequently because sweating can cause symptom exacerbations.¹⁸ In the occupational setting, a variety of chemicals may be encountered. To determine the most appropriate protective glove for a specific chemical, it may be necessary to consult with workplace management or visit <http://www.ansellpro.com/specware> for guidance and more information regarding which gloves are appropriate for certain occupational chemicals.¹⁵ Antiimpaction gloves have been shown to help patients with frictional hand dermatitis return to work.⁴³ Barrier creams, which place a physical barrier between the skin and potential irritants, may also be of use in occupations with chemical exposures.⁴⁴

The most basic substitution involves using mild soaps or soap substitutes and bland emollients. The aggressive use of emollients is critical to improving the skin's barrier function and providing the skin with adequate hydration.^{31,45} Simple petroleum-based emollients are generally as effective as newer emollients that contain skin-related lipids.⁴⁵

Medical therapy

Although lifestyle changes help in many instances to ameliorate the symptoms of hand dermatitis, medical treatment is generally necessary to gain further symptomatic control.

TREATMENTS THAT HAVE BEEN SHOWN TO BE EFFECTIVE FOR CHRONIC HAND DERMATITIS

Methods

Search Methodology

The electronic databases (Medline, Embase, and PubMed) were searched from January 1980 to December 2009 using the terms "hand dermatitis"/"hand eczema" and treatment. Additional papers cited by major articles written on hand dermatitis that pertained to the search criteria were included for screening.

Study Selection and Inclusion/ Exclusion Criteria

Titles, abstracts, and where necessary, full texts were read by one researcher and included if they dealt with hand dermatitis and the results of a therapeutic intervention. Single case reports and reviews were excluded, but case series and open-label studies were considered alongside randomized controlled studies. Studies that focused more on lifestyle changes, preventative measures, and emollients were excluded, along with studies that focused solely on the treatment of nickel-related hand dermatitis. Full texts were then reviewed.

Main outcome measures

Primary outcome measure assessed was the reduction in hand dermatitis symptoms. Additional measures assessed were rates of relapse and the severity and frequency of therapy-related adverse events.

Results

Included studies

48 studies specific to the treatment of hand dermatitis were identified. These studies involved a total of 3036 subjects. Of these 48 studies, 27 were open-label, 19 were double-blinded, one was single blinded, and one was a case-series. Placebo-control was included in the methods of 13 papers. Assessment periods ranged from two weeks to 1 year. Thirty papers evaluated patients with chronic hand dermatitis, 11 papers studied vesicular hand dermatitis, two papers assessed occupational-related hand dermatitis, two evaluated hyperkeratotic hand dermatitis, two studied exclusively atopic hand dermatitis, and one studied allergic contact hand dermatitis. (Chronic hand dermatitis [CHD] is generally defined as hand dermatitis symptoms lasting longer than 6 months).⁴²

TOPICAL AGENTS

Topical Steroids

Topical steroids are generally the first treatment tried for hand dermatitis. Four papers evaluated topical corticosteroids, two studied steroids in the primary reduction of hand dermatitis symptoms, and another two assessed intermittent steroid use for maintaining symptom remission. Additionally, one paper evaluated using zinc sulphate to augment corticosteroids' effect (Table 10-1).

Efficacy

One study of 61 patients with CHD found that continuous treatment with clobetasol propionate (group I steroid) for

a period of 1 to 3 weeks brought about healing in 90% of patients (mean time to healing was 11 days).⁴⁶

Two studies, with a total of 165 patients, compared the efficacy of various topical steroid strengths (group II to group V) for the primary reduction of hand dermatitis symptoms.^{47,48} Both studies revealed no difference in therapeutic effect between the topical steroids evaluated ($p>0.06$ as reported by Fowler et al.⁴⁷).

One paper performed a double-blind, left/right comparison study of 47 patients and found that the addition of 2.5% zinc sulphate to 0.05% clobetasol significantly decreased hand dermatitis symptoms and recurrence rates ($p<0.05$).⁴⁹

Adverse Events

Only minor effects, such as burning sensations, reversible skin atrophy, and brittle skin were noted with treatment.⁴⁶ Systemically, headache and jitteriness were recorded.⁴⁷ Side effects occurred with similar frequency between very strong potency and medium potency topical steroids.⁴⁶

Relapse

Two papers assessed the intermittent use of topical steroids for maintaining symptom remission. Veien et al.⁵⁰ found that clearance persisted in 83% and 68% when mometasone furoate was applied 3 times/week or 2 times/week, respectively, compared to 26% of the control ($p=0.001$). Moller et al.⁴⁶ found intermittent use of a very strong topical corticosteroid (clobetasol propionate) kept a higher percentage (70%) of patients in remission than a medium potency corticosteroid (fluprednidene acetate) (30%).

Nonsteroidal Immunomodulators

Six studies were found that evaluated the topical calcineurin inhibitors, tacrolimus and pimecrolimus, in patients with hand dermatitis (Table 10-2).

Efficacy

Two open, noncontrolled studies assessed the use of tacrolimus ointment 0.1%. In the first study, 29 patients with occupational hand dermatitis who applied tacrolimus twice daily had a significant reduction in severity after 12 weeks, with 44% achieving clear skin ($p<0.001$).⁵¹ The second study assessed thrice daily application of tacrolimus for 8 weeks in patients with CHD and found that except for vascularization, there were significant improvements in composite severity, erythema, scaling, induration, fissuring, and pruritus ($p<0.007$).⁵²

Pimecrolimus cream 1% was assessed in one open, noncontrolled study in 13 patients with CHD who applied the cream twice daily. Results showed that 85% of the

TABLE 10-1—Selected* Studies of Topical Corticosteroids for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Fowler, 2005 ⁴⁷	Double-blind, randomized, L/R comparison	Hydrocortisone butyrate 0.1% cream vs. fluticasone propionate 0.05% cream, prednicarbate 0.1% cream, or mometasone furoate 0.1% cream	BID application	2 weeks	89	CHD	All steroids improved symptoms from baseline ($p<0.02$), with no difference in efficacy between steroid pairings ($p>0.06$).	Headache and jitteriness (1/89, 1%), mild itching (1/89, 1%)	—
Bleeker, 1989 ⁴⁸	Double-blind, comparative trial	Corticoderm cream + unguentum emollient vs. betnovate (betamethasone) cream + unguentum emollient	Once daily application	3 weeks	76	ACD, ICD, AD	No difference observed between the two treatment arms.	—	—
Veien, 1999 ⁵⁰	Open, randomized, controlled	After inducing remission with daily mometasone furoate, patients were randomized to receive maintenance mometasone therapy 3x/week, 2x/week, or not at all.	Per treatment group	Up to 36 weeks	120	CHD	Clearance persisted in 83%, 68%, and 26% of the 3x/week, 2x/week, and no steroid applied groups, respectively ($p=0.001$).	Mild skin atrophy (10/120, 8%)	—
Moller, 1983 ⁴⁶	Double-blind, L/R comparison	After inducing remission with clobetasol, maintenance therapy compared clobetasol propionate and fluprednidene acetate	2 applications/ week	Mean: 138 days	61	CHD	55/61 (90%) healed with clobetasol.	Burning sensation (4/55, 7%), brittle skin (2/55, 4%), reversible skin atrophy (1/55, 2%)	Maintenance therapy prevented relapses in 70% with clobetasol, 30% with fluprednidene.
Faghhihi, 2008 ⁴⁹	Double-blind, randomized, L/R comparison	Clobetasol 0.05% + zinc sulphate 2.5% cream vs. clobetasol 0.05% alone	BID application	2 weeks	47	CHD	Clobetasol + zinc was more effective than clobetasol alone ($p<0.05$).	None observed	—

*Please refer to methods in main text regarding search criteria and how papers were selected.
CHD—chronic hand dermatitis; ACD—allergic contact dermatitis; ICD—irritant contact dermatitis; AD—atopic dermatitis

TABLE 10-2—Selected* Studies of Topical Immunomodulators for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Schliemann, 2008 ⁵¹	Open, not controlled	Topical Tacrolimus 0.1%	BID application	4 weeks	29	Occupational hand dermatitis	Significant improvement in severity from baseline ($p<0.001$); 44% achieved clearance.	Relapse of herpes labialis (2/29, 7%); flushing (1/29, 3%); transient burning (5/29, 17%); itching (5/29, 17%); erythema (3/29, 10%)	—
Krejci-Manwaring, 2008 ⁵⁶	Double-blind, randomized, placebo-controlled	Topical Tacrolimus 0.1% ointment vs. vehicle control	BID application	12 weeks	32	CHD	Treatment significantly improved induration and scaling ($p=0.003$ for both), but did not significantly prolong time to recurrence ($p=0.78$).	—	69% of responders relapsed.
Thelmo, 2003 ⁵²	Open, not controlled	Topical Tacrolimus 0.1%	TID application	8 weeks	25	CHD	Significant improvement in severity from baseline ($p<0.007$).	Mild transient burning at application site (5/25, 20%)	—
Belsito, 2004 ⁵⁵	Double-blind, randomized, placebo-controlled	Pimecrolimus 1% cream vs. vehicle control	BID application	22 days	294	CHD	Trend toward clearance with treatment ($p=0.068$)	Application site burning (0.7%)	—
Thaci, 2003 ⁵³	Open, not controlled	Pimecrolimus 1% cream	BID application	22 days	13	CHD	85% improved from baseline (11/13)	Application site burning (4/13, 31%), pruritus (2/13, 15%)	—
Baskan, 2007 ⁵⁴	Double-blind, randomized, L/R comparison, placebo-controlled	Pimecrolimus 1% cream vs. control	BID application	8 weeks	25	CHD	Significant improvement with treatment over placebo ($p=0.04$).	None observed.	—

*Please refer to methods in main text regarding search criteria and how papers were selected.
CHD—chronic hand dermatitis; ACD—allergic contact dermatitis; ICD—irritant contact dermatitis; AD—atopic dermatitis

patients improved from baseline.⁵³ Two double-blind, randomized, controlled trials also assessed the twice daily application of pimecrolimus. Baskan et al.⁵⁴ performed a left versus right comparison study of 25 patients with CHD and found that the treated hand improved significantly over the controlled hand ($p=0.04$), with symptoms of erythema, desquamation, lichenification, edema, and fissuring improving; the treatment did not appear to be effective for vascularization. However, Belsito and colleagues⁵⁵ performed a larger vehicle-controlled study of 294 patients treated over 3 weeks with pimecrolimus and failed to find significance with treatment ($p=0.068$).

Adverse Effects

Topical tacrolimus most commonly caused transient burning, itching, and redness at the application site, which decreased with use.^{51,52} Reactivation of herpes labialis was seen in two patients.⁵¹ Topical pimecrolimus most commonly caused application site burning and pruritus.^{53,55}

Relapse

Krejci-Manwaring and colleagues⁵⁶ assessed the use of topical tacrolimus 0.1% in 32 subjects with CHD who had received a 3-week prednisone taper and found that 69% of patients relapsed. The time to relapse was 48 days with tacrolimus compared to 39 days with vehicle ($p=0.78$).⁵⁶ Relapse was not assessed with pimecrolimus.

Topical Retinoids

One study, a phase I-II trial, was found, which assessed the efficacy of topical retinoids in patients with hand dermatitis (Table 10-3).

Efficacy

Hanifin and colleagues⁵⁷ studied the efficacy and safety of bexarotene gel in 55 patients with severe CHD. Patients

were randomized to either bexarotene gel 1% alone, or bexarotene gel 1% in combination with one of two topical steroids. Overall, 36% of patients achieved >90% clearance of hand dermatitis, and 71% achieved >50% clearance. Response rates did not improve with topical steroid use. Monotherapy seemed to be particularly effective for patients with irritant dermatitis.⁵⁷

Adverse Events

Irritation, moderate stinging, and burning with application were the most common complaints. Flaring of the dermatitis occurred in several patients (most commonly in patients with atopic dermatitis).⁵⁷

Relapse

Few patients relapsed once response was achieved, with responses persisting after discontinuation of the medication through 4 weeks of follow-up.⁵⁷

Ionizing Radiation

Two forms of radiation are most frequently used in the treatment of hand dermatitis, conventional superficial x-rays and Grenz rays (ultra-soft x-rays or Bucky rays). Seven papers were found which assessed ionizing radiation on a total of 148 patients (Table 10-4).

Efficacy

CONVENTIONAL SUPERFICIAL X-RAYS

Farris et al.⁵⁸ studied superficial x-ray therapy compared to a placebo-control in a double-blind study of 24 patients with hand dermatitis and found therapy led to a significant reduction in symptoms as assessed by both the patient and the observer. King and Chalmers,⁵⁹ however, found that patients with hyperkeratotic hand dermatitis or pompholyx who were treated with superficial radiotherapy

TABLE 10-3—Selected* Study of a Topical Retinoid for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Hanifin, 2004 ⁵⁷	Open, randomized	Bexarotene gel 1% alone vs. bexarotene gel 1% + mometasone furoate ointment 0.1% vs. bexarotene gel 1% + topical hydrocortisone ointment 1%	TID application, as tolerated	22 weeks, as tolerated	55	CHD	36% of patients achieved > 90% clearance of hand dermatitis; 71% achieved > 50% clearance	Irritation at application site (16/55, 29%), stinging/burning (8/55, 15%), dermatitis flare (9/55, 16%)	'few'

*Please refer to methods in main text regarding search criteria and how papers were selected.

CHD—chronic hand dermatitis; ACD—allergic contact dermatitis; ICD—irritant contact dermatitis; AD—atopic dermatitis

TABLE 10-4—Selected* Studies of Ionizing Radiation for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Farris, 1984 ⁵⁸	Double-blind, randomized, placebo-controlled, L/R comparison	Superficial radiotherapy vs. control	100 rad at 50kV at 3 week intervals	3 treatments	24	CHD	Significant reduction in symptoms as reported by both the patient and observer.	—	—
King, 1984 ⁵⁹	Double-blind, randomized, placebo-controlled, L/R comparison	Superficial radiotherapy vs. control	100 rad given 1 week apart	3 treatments	15	Hyperkeratotic hand dermatitis, pompholyx	At one month 7/15 (46%) of treated hands improved vs. none of control ($p<0.01$). At 3 and 6 months, no difference between treatment and placebo.	—	3/7 (43%) of initial responders relapsed within 2 months.
Sheehan-Dare, 1989 ⁶⁰	Single-blinded, randomized L/R, controlled	PUVA + mock-radiotherapy vs. superficial radiotherapy + mock PUVA	Radiotherapy: 3 treatments (0.9 Gy at 600kV) at 21 day intervals; PUVA: 1% 8-methoxysoralen + UVA 15 J/cm(2) 3x/week	Radiotherapy: 9 weeks; PUVA: 6 weeks	21	CHD	At 18 weeks, both therapies had led to improvement in the dermatitis; superficial radiotherapy produced a significant drop in symptom severity scores ($p=0.013$), but no difference between the two therapies was noted clinically.	—	—
Cartwright, 1987 ⁶¹	Double-blind, L/R, placebo-controlled	Grenz ray vs. control	300 rad (3 Gy) of Grenz rays: 3 treatments at 3 week intervals	18 weeks	30	CHD	No difference between treatment and placebo ($p>0.05$)	Pigmentation of treated hand (1/30, 3%)	—
Lindelof, 1987 ⁶²	Double-blind, placebo-controlled, L/R comparison	Grenz ray vs. control	300 rad (3Gy) given at 1 week intervals	6 treatments	24	CHD	Significant improvement with Grenz ray therapy ($p<0.001$ at 10 weeks).	Slight pigmentation (5/24, 21%)	—
Farris, 1985 ⁶³	Double-blind, randomized, L/R comparison	Conventional superficial X-ray vs. Grenz ray	100 rad (1Gy) conventional superficial X-ray on one hand, 300 rad (3 Gy) Grenz ray on the other. Treatments given 3 weeks apart.	3 treatments	25	CHD	Mean grade of eczema was significantly better at all stages with superficial x-rays ($p<0.05$).	None observed	—
Duff, 2006 ⁶⁴	Open, not controlled	Megavoltage radiation	900-1200 cGy	varied	9	Chronic vesicular hand dermatitis	All patients improved from baseline. 73% resolved completely.	—	20% recurred after complete resolution; 47% remained completely resolved.

*Please refer to methods in main text regarding search criteria and how papers were selected.
CHD—chronic hand dermatitis; ACD—allergic contact dermatitis; ICD—irritant contact dermatitis; AD—atopic dermatitis

showed significant improvement at one month over control ($p<0.01$), but at 3 and 6 months, significance was not maintained. Sheehan-Dare and colleagues⁶⁰ compared superficial radiotherapy to topical PUVA in a double-blind study of 21 CHD patients, and found that superficial radiotherapy led to more rapid improvement and a significant decrease in symptom severity scores ($p=0.013$ at 18 weeks). Both modalities led to improvement from baseline, but no difference between the two was clinically apparent at 18 weeks.⁶⁰

GRENZ RAYS

One double-blind trial compared Grenz ray therapy (300 rad given every 3 weeks) to placebo in 30 patients, and found Grenz ray therapy to be no more effective than placebo for CHD.⁶¹ However, Lindelof et al.⁶² used weekly Grenz ray therapy (300 rad) in 24 patients with CHD therapy and found it led to significant improvement over control ($p<0.01$ at 10 weeks).

Farris et al.⁶³ compared 300 rad of conventional superficial x-rays to 900 rads of Grenz rays in a double-blind trial with 25 hand dermatitis patients and found treatment with superficial x-rays led to better outcomes ($p<0.05$).

MEGAVOLTAGE RADIATION

One open, noncontrolled study assessed megavoltage radiation therapy in 9 patients with chronic vesicular hand dermatitis. All patients improved during the course of the radiation, with 47% of the sites irradiated completely clearing.⁶⁴

Adverse Events

Only skin pigmentation was noted with Grenz ray treatment.^{61,62}

Relapse

43% of patients who initially responded to superficial x-rays relapsed within 2 months.⁵⁹ Twenty percent of patients treated with megavoltage radiation relapsed after completely clearing.⁶⁴

Phototherapy

Both UVA and UVB have been used in the treatment of hand dermatitis. Twenty papers were found which evaluated phototherapy in the treatment of hand dermatitis (Table 10-5).

UVA

UVA-1 phototherapy utilizes long-wave UVA radiation (340-400nm) and has been shown to be effective in treating several inflammatory skin diseases.⁶⁵

Efficacy

One open, noncontrolled study evaluated the effectiveness of local UVA-1 irradiation in the treatment of 12 patients with chronic vesicular hand dermatitis. Patients received 40 J/cm² of UVA-1 daily to their hands for 3 weeks. Ten of the twelve patients significantly improved from pretreatment levels with therapy ($p=0.002$).⁶⁶ These results were supported by a double-blind, randomized study of 28 patients with vesicular hand dermatitis who received either UVA-1 or placebo. Treatment with UVA-1 was found to be significantly more effective than placebo in reducing symptoms ($P=0.005$).⁶⁷

Adverse Events

Mild erythema was the only adverse event observed.⁶⁷

Relapse

Three month post-treatment assessments revealed no relapse in patients that responded to UVA-1 therapy.⁶⁶

PUVA

Psoralen plus UVA (PUVA) combines a photosensitizer (psoralen) with UVA phototherapy. Psoralen can be given topically or orally.

Efficacy

Three open, noncontrolled studies assessed oral PUVA in a total of 54 patients with hand dermatitis. One study of 38 CHD patients found 20 cleared with treatment (53%),⁶⁸ while another study found six of nine (67%) achieved clearance after an average of 23 treatments (150 J/cm²).⁶⁹ The third paper studied oral PUVA in seven patients with severe recurrent vesicular (dyshidrotic) dermatitis and reported 100% clearance with their treatment and maintenance regimen.⁷⁰

Additionally, four open, noncontrolled studies assessed topical PUVA. Two studies, by Schempp et al.⁷¹ and Davis et al.⁷² evaluated bath PUVA with 8-MOP and found improvement in 93% and 70%, with 64% and 41% clearing, respectively. One study assessed PUVA with directly applied 0.1% 8-methoxysoralen in 17 CHD patients and found clinical improvement of at least moderate quality was observed in 82% of patients, with 29% having significant improvement.⁷³ The last study compared the use of paint PUVA with a cream to bath PUVA and found that a greater percentage of patients with hyperkeratotic hand dermatitis responded to the cream than the bath (75% versus 50%, respectively).⁷⁴

Oral PUVA therapy was compared to topical PUVA in two papers. Hawk and Grice⁷⁵ found that oral PUVA led to similar clearance rates in patients with dermatitis: 60% for

TABLE 10-5—Selected* Studies of Phototherapy for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Schmidt, 1998 ⁶⁶	Open, not controlled	UVA-1	Five 40 J/cm(2) treatments/ week	3 weeks	12	Chronic vesicular hand dermatitis	Almost complete clearing in 10/12 patients (83%) ($p=0.002$)	None observed	Those who cleared had no relapse within 3 months.
Polderman, 2003 ⁶⁷	Double-blind, randomized, placebo-controlled	UVA-1 vs. control	Five 40 J/cm(2) treatments/ week	3 weeks	28	Vesicular hand dermatitis	UVA-1 significantly more effective than placebo ($p=0.005$ at 3 weeks).	Mild erythema	—
LeVine, 1981 ⁷⁰	Open, not controlled	Oral PUVA (UVA to right hand only initially, then to both)	8-methoxypsonalen 0.6mg/kg p.o. + UVA (initial dose 2.5J/cm(2), increased by 0.5-1.0J/cm(2) until clear (mean max dose: 23 J/cm(2))). Treatments given 3x/week until clear. Patients then placed on maintenance schedule and dose (80% of max or 20 J/cm(2)) to sustain remission.	Mean number of treatments: 31.4	7	Severe vesicular (dyshidrotic) hand dermatitis	All patients cleared with treatment.	—	Two patients with no maintenance therapy were still clear at four and six months, respectively.
Bruynzeel, 1982 ⁶⁹	Open, not controlled	Oral PUVA	8-methoxypsonalen 0.5-0.6mg/kg p.o. + UVA (total dose 104-210 J/cm(2), mean: 150 J/cm(2)). Treatments given 2x/week.	varied	9	ACD	6/9 (67%) cleared with treatment	Mild erythema and slight nausea in "some"	If treatment stopped, relapsed occurred ~12-17 weeks later.
Tegner, 1985 ⁶⁸	Open, not controlled	Oral PUVA	8-methoxypsonalen 0.6mg/kg p.o. + UVA (initial dose 2.5 J/cm(2) increased by 0.5 J/cm(2) every other session. Mean total dose: 73 J/cm(2)). Treatments given 3x/week. Maintenance therapy initiated in 13 patients.	Mean number of treatments: 19	38	CHD	Total clearance: 20/38 (53%), an additional 11/38 (29%) were improved.	Nausea (8/38, 21%), verrucae vulgaris (2/38, 5%), pruritus (1/38, 3%)	Mean remission time: 11 months
Schempp, 1997 ⁷¹	Open, not controlled	Local bath PUVA	15 minute soak of 0.15% 8-MOP solution added to tap water for a final concentration of 1 mg 8-MOP/L, followed by initial dose of 0.5 J/cm(2) UVA increased by 0.5-1.0 J/cm(2), as tolerated.	Therapy discontinued after 25 treatments, when clear, or by request.	14	Chronic vesicular dermatitis, chronic hyperkeratotic dermatitis	13/14 (93%) showed considerable improvement; complete clearance in 9/14 (64%)	None observed	Average disease-free interval was 6 months.

(Continued)

TABLE 10-5—Selected* Studies of Phototherapy for Hand Dermatitis (Continued)

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Davis, 1998 ⁷²	Open, not controlled	Local bath PUVA	30 minute soak of 0.0005% methoxsalen solution + UVA (initial dose 0.5 J/cm ²), increased by 0.5 J/cm ² to a max dose of 10 J/cm ² . Mean total UVA dose: 140 J/cm ²). Treatments given 3x/week until maximal improvement, then tapered.	Mean number of treatments: 27.3	CHD (5 chronic vesicular)	12/17 (70%) improved, with 7/17 (41%) clearing	Mild erythema. Blistering in 1 patient.	—
Grittyarangsang, 1998 ⁷³	Open, not controlled	Local PUVA	Topical 0.1% 8-methoxysoralen + UVA (Mean dose: 63.5 J/cm ²)	Mean number of treatments: 22.2	CHD	At least moderate improvement in 14/17 (82%), 5/17 (29%) showing significant improvement.	Erythema and burning that improved with lower dose (3/17, 18%).	"High" rate of relapse within a few months after treatment discontinuation.
Grundmann-Kollmann, 1999 ⁷⁴	Open, randomized, L/R comparison	PUVA-bath vs. PUVA-cream	1 hour application of 0.0006% 8-MOP cream vs. 20 minute soak of 0.5 g of 8-MOP in 100 ml 96% ethanol diluted in warm water to 0.5mg 8-MOP/L. UVA: 0.3-0.5 J/cm ² initial dose to max 3.5-6.0 J/cm ² . 4 treatments/week	Mean number of treatments: PUVA-bath = 18, PUVA-cream = 27.	AD, Hyperkeratotic Hand Dermatitis	50% of patients with hyperkeratotic hand dermatitis responded with PUVA-bath, 75% responded with PUVA-cream.	Blistering, severe erythema, hyperpigmentation	Those who responded continued without relapse for up to 8 weeks.
van Coevorden, 2004 ⁷⁶	Open, randomized	Oral PUVA at home vs. hospital bath PUVA	Home: methoxsalen 0.6mg/kg p.o. + UVA 0.54-8.1 J/cm ² (max) 3x/week Hospital: bath with trioxsalen 0.2mg/L for 15 minutes + UVA 0.59-20 J/cm ² (max) 2x/week	10 weeks	CHD	Both groups showed significant improvements from baseline ($p < 0.001$); there was no significant difference in improvement between the two groups ($p=0.15$)	Nausea with oral PUVA (3/78, 4%); mild stinging with bath PUVA (1/80, 1%)	—

Hawk, 1994 ⁷⁵	Open, not randomized	Oral PUVA vs. Topical PUVA	Oral PUVA: 8-methoxysoralen 0.6 mg/kg p.o. + UVA (initial dose 0.5-2.5 J/cm(2) depending on skin type, increasing by 0.5-2.0 J/cm(2) at each treatment as tolerated, to max dose of 15 J/cm(2)). Topical PUVA: 15-30 minute treatment of 8-MOP emulsion + UVA (initial dose 0.25-1.25 J/cm(2) depending on skin type, increased by 0.25-1.05 J/cm(2) at each treatment as tolerated, to max dose of 15 J/cm(2)). Treatments give 2x/week.	Mean number of treatments (for all dermatoses): 22 for oral PUVA, 24 for topical PUVA	7	CHD	Oral PUVA: 3 / 5 (60%) improved; 2/5 (40%) completely cleared. Topical PUVA: 1/2 (50%) completely cleared.	—
Grattan, 1991 ⁸⁰	Double-blind, randomized, placebo-controlled L/R comparison	Topical PUVA vs. UVA + topical placebo control	PUVA: 0.1% 8-methoxysoralen + UVA. UVA: Starting dose 0.5 J/cm(2) increased by 0.5 J/cm(2) to a max of 12 J/cm(2). Treatments given 3x/week. Overall mean dose = 105.5 J/cm(2).	8 weeks	12	Chronic vesicular hand dermatitis	Flaring of the dermatitis (2/12, 17%), mild burning (1/12, 8%)	Both treatment arms improved from baseline ($p<0.005$), but there was no significant difference between the two groups.
Adams, 2007 ⁷⁹	Open, randomized, L/R comparison	Topical PUVA vs. UVA-1	PUVA: 0.001% 8-methoxysoralen cream + UVA (cumulative dose: 17.4 J/cm(2)) 3x/week; UVA: 40 J/cm(2) (cumulative dose: 600 J/cm(2)) 3x/week	5 weeks	15	Chronic vesicular hand dermatitis	Both PUVA and UVA led to significant improvements from baseline ($p=0.0039$ and 0.049, respectively), but there was no significant difference between the two treatments ($p=0.31$).	—
Simons, 1997 ⁸⁵	Open, randomized, L/R comparison	UVB vs. topical bath PUVA	UVB: 2.9-3.6 mW/cm(2), 3x/week; PUVA: trioxsalen 0.1mg/mL 15 minute soak + UVA 7.2-8.2 mW/cm(2), 2x/week	6 weeks	13	CHD	Both PUVA and UVB led to significant improvements from baseline ($p<0.05$ in both), but there was no significant difference between the two treatments ($p>0.05$)	—

(Continued)

TABLE 10-5—Selected* Studies of Phototherapy for Hand Dermatitis (Continued)

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse	
Rosen, 1987 ⁷⁸	Randomized, L/R controlled	PUVA + control vs. UVB + control	PUVA: 8-methoxypсорален 0.6 mg/kg p.o. + UVA (initial dose 2 J/cm ²) increased by 0.5-1.0 J/cm ² as tolerated to a max of 15 J/cm ²). Mean total dose: 100 J/cm ² UVB: Initial dose 30 mJ/cm ² increased to 840 mJ/cm ² as tolerated. Mean total dose: 11,000 mJ/cm ² . Treatments given 3x/week.	Until clearance or a maximum 3 months	35	CHD	PUVA treated hands improved significantly over UVB ($p<0.001$). PUVA: All treated hands cleared and were significantly improved over untreated hands ($p<0.001$). UVB: Treated hand significantly more improved than untreated ($p<0.05$); no hands cleared.	PUVA: Nausea (29%), edema, pain, pruritis (21%), flare of dermatitis (21%), reversible hyperpigmentation (7%) UVB: Palmar bullae (12.5%), Staph. Aureus infection (6%) Significantly more adverse effects with PUVA than UVB ($p<0.0001$).	9/14 (64%) who cleared with PUVA relapsed within 3 months.
Sezer, 2007 ⁷⁷	Open, L/R comparison	UVB vs. topical paint PUVA	UVB: initial 150 mJ/cm ² , increasing to 2000 mJ/cm ² , 3x/week; PUVA: 0.1% 8-methoxypсорален gel + UVA 1.0 J/cm ² increasing to 7.5 J/cm ² 3x/week	9 weeks	12	CHD	Both topical paint PUVA and UVB led to significant improvements from baseline ($p=0.002$ in both), but there was no significant difference between the two treatments ($p=0.552$).	Mild xerosis responsive to emollients was seen in both groups, hyperpigmentation with PUVA (3/15, 2%), exacerbation of dermatitis (1/15, 7%)	UVB: 33% relapsed; paint PUVA: 50% relapsed
Kuhl, 2008 ⁸¹	Open, not randomized	Narrowband UVB	Initial 60-200 mJ/cm ² NB-UVB increased as patient tolerated. Mean total dose: 28,848 mJ/cm ² . 2-3 treatments per week.	Mean treatment duration: 3.25 months	8	CHD	7/8 (88%) showed a clinical response, with 2/8 (25%) having disease clearance	1/8 (13%) photoerythema, 1/8 (13%) pruritus & tingling.	
Bayerl, 1999 ⁸³	Open, randomized, controlled	Home UVB vs. control	UVB: back of hands 0.1 mW/m ² , palms 0.13 mW/m ²	2 months	48	Occupational hand dermatitis	Improvement with UVB was not significant	Stinging & burning; exacerbation of dermatitis (2/48, 42%)	

Sjovall, 1987 ⁸²	Open-label	Home UVB vs. Clinic UVB	Palms: 380 mJ/cm(2) increased to a max of 2900 mJ/cm(2). Dorsal hand: 100 mJ/cm(2) increased to a max of 1200 mJ/cm (2). Treatments were 4-5x/week.	10-15 weeks	26	CHD	18/26 (69%) were improved; a parallel and significant drop in both groups ($p<0.01$); none cleared	Burning and stinging (6/26, 23%)
Sjovall, 1994 ⁸⁴	Double-blind, randomized, placebo-controlled	Hand UVB vs. Whole body + Hand UVB vs. control	Palmar Hand: initially 100 mJ/cm(2) increased to 1300 mJ/cm(2) (cumulative dose ~ 19,000 mJ/cm(2)); Dorsal Hand & Whole Body: initially 25 mJ/cm(2) increased to 1000 mJ/cm (2) (cumulative dose ~ 13,000 mJ/cm(2)); Treatments 4x/week	8 weeks	18	CHD	Significant improvement is found only between whole body + hand UVB & placebo ($p<0.05$)	—

*Please refer to methods in main text regarding search criteria and how papers were selected.

CHD-chronic hand dermatitis; ACD-allergic contact dermatitis; ICD-irritant contact dermatitis; AD-atopic dermatitis

oral PUVA versus 50% for topical PUVA. Van Coevorden and colleagues⁷⁶ compared oral PUVA at home to topical bath PUVA administered in a hospital in 158 patients, and after 10 weeks of treatment, both groups showed equally substantial clinical improvement in their hand dermatitis ($p<0.001$), and there was no significant difference between the treatment modalities ($p=0.15$).

Adverse Effects

Oral PUVA commonly caused nausea.^{68,69} Topical PUVA was associated with stinging, burning, erythema, blistering, flaring of the dermatitis, and reversible hyperpigmentation.^{72-74,76}

Relapse

Once weekly maintenance therapy was generally necessary to remain asymptomatic after treatment with oral PUVA.⁷⁰ If patients discontinued treatment, remission continued for roughly 3 to 6 months,^{69,70} although one study reported a mean remission time of 11 months.⁶⁸ Relapse rates with topical PUVA were approximately 50-65%,^{77,78} with time to relapses varying from 2 to 6 months.^{71,74,78}

Comparative efficacy

Two studies compared topical PUVA to UVA therapy in patients with chronic vesicular hand dermatitis. In one open-label, left/right comparison study, both PUVA and UVA led to significant improvements from baseline ($p=0.0039$ and 0.049 , respectively), but there was no significant difference between the two treatments ($p=0.31$).⁷⁹ This data is supported by a double-blind study where 12 patients were randomized to receive either PUVA or UVA. Again, both treatment modalities led to significant symptom reductions from baseline ($p<0.005$), but there was no statistical difference between the two treatments.⁸⁰

UVB

Efficacy

One open-label study assessed narrowband-UVB in the treatment of eight CHD patients who were unresponsive to other forms of therapy. Results showed 88% improved, with 25% achieving complete clearance of lesions.⁸¹ Local (hand) versus whole-body UVB therapy was assessed in one double-blind, randomized, placebo-controlled trial with 18 CHD patients. Results revealed significant improvement only with whole-body UVB therapy compared to placebo, not with local hand UVB therapy.⁸²

Two open-label studies assessed home-UVB therapy. Bayer et al.⁸³ randomized 48 patients to either receive home UVB radiation or a placebo-control. Clinical

improvement with therapy was not found to be significant over control. However, Sjovall et al.⁸⁴ in their open-label study found home Hydrolux UVB units were as effective in the treatment of hand dermatitis as clinic units, with both significantly improving symptoms from baseline ($p<0.01$ in both).

Adverse Effects

Mild xerosis, stinging/burning, pruritus, erythema, palmar bullae, and exacerbation of dermatitis were reported with UVB use.^{78,81,83,84}

Relapse

One study reported that 33% of patients relapsed after treatment with UVB.⁷⁷

Comparative efficacy

UVB was compared to topical PUVA in three left versus right open-label studies. All three studies found that both UVB and PUVA led to significant improvements in disease severity from baseline ($p=0.002$ for both treatments, as reported by Sezer and Etikan⁷⁷). When comparing the efficacy of the two treatment modalities, two studies^{77,85} found there to be no significant difference between PUVA and UVB ($p=0.552$, p-values as reported by Sezer and Etikan⁷⁷), while the third study found PUVA led to significantly better outcomes than UVB ($p<0.001$).⁷⁸

SYSTEMIC THERAPIES

Cyclosporine

Cyclosporine is an immunosuppressant drug and potent T-cell inhibitor. One paper assessed cyclosporine for use in hand dermatitis (Table 10-6).

Efficacy

In a double blind trial, 41 patients with hand dermatitis were treated with either cyclosporine (3 mg/kg/day) or a potent topical corticosteroid for 6 weeks. Both treatments significantly improved the dermatitis from baseline ($p<0.001$ for both groups), and there was no significant difference in efficacy between the two treatment groups.⁸⁶

Adverse Events

Adverse events occurred in 68% of patients receiving cyclosporine compared to 56% of patients receiving the topical steroid. Cyclosporine led to an increased creatinine 30% above baseline in 5% of patients. There were no occurrences of hypertension.⁸⁶

TABLE 10-6—Selected* Studies of Cyclosporine, Methotrexate, and Oral Retinoids for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	N	Hand Dermatitis Type	Efficacy	Adverse Events Related to Treatment	Relapse
Granlund, 1996 ⁸⁶	Double-blind, randomized, comparison trial	Oral cyclosporine vs. topical betamethasone-17,21-dipropionate 0.05%	Cyclosporine 3 mg/kg/day	6 weeks	41	CHD	Both treatment arms led to improvement from baseline ($p<0.001$ in both), but there was no significant difference between treatment modalities.	19/28 (68%) of patients on cyclosporine had some kind of adverse event (non-specific); increased creatinine 30% above baseline, but normalized with decreased dose in 2/41, 5%	50% relapsed within 2 weeks
Egan, 1999 ⁸⁷	Case series	Methotrexate	12.5-22.5 mg/week	varied	5	Vesicular Hand Dermatitis	All five patients cleared with treatment.	—	—
Bollag, 1999 ⁸⁸	Open, not controlled	Alitretinoin (9-cis-retinoic acid)	20 or 40 mg daily	1-5 months (mean: 2.3 months)	38	CHD	95% of patients showed clinical improvement, 55% with a very good response. All forms of HD responded similarly.	Transient headache (4/38, 11%), cheilitis (1/138, 29%), transient flushing (4/38, 11%), conjunctivitis (1/38, 3%)	Relapse occurred 1 month to 1 year later
Ruzicka, 2004 ⁸⁹	Double-blind, randomized, placebo-controlled	Alitretinoin vs. control	10 mg/day, 20 mg/day, or 40 mg/day	12 weeks	319	CHD	Alitretinoin led to significant improvement in all types and severities of CHD over placebo ($p<0.001$)	Headache (34/241, 14%); dry mouth/lips/mucosa (15/241, 6%); one patient developed erysipelas requiring hospitalization	26% relapsed
Ruzicka, 2008 ⁹⁰	Double-blind, randomized, placebo-controlled	Alitretinoin vs. control	10 gm/day or 30 mg/day	24 weeks	1032	CHD	48% of patients treated with alitretinoin had clear or almost clear hands, compared to 17% of placebo ($p<0.001$)	Headache (96/827, 11%), dry mouth/lips/skin (59/827, 7%), hyperlipidemia (9%), decreased TSH (6%)	Mean time to relapse: 5.5-6.2 months

*Please refer to methods in main text regarding search criteria and how papers were selected.

CHD=chronic hand dermatitis; ACD-allergic contact dermatitis; ICD-irritant contact dermatitis; AD-atopic dermatitis

Relapse

After 2 weeks, relapse rates were roughly 50% in both groups.⁸⁶

Methotrexate

Methotrexate is a cytotoxic drug commonly used to control severe recalcitrant inflammatory dermatoses. One paper assessed methotrexate in hand dermatitis (Table 10-6).

Efficacy

In one case series, Eagan et al.⁸⁷ used low-dose methotrexate (12.5 to 22.5 mg per week) in five patients with severe vesicular hand dermatitis and found that all five patients either partially or completely cleared.

Adverse Events & Relapse

Neither adverse events nor relapses were documented in this case series.

Oral Retinoids

One oral retinoid, alitretinoin (9-cis-retinoic acid), was evaluated in three papers for use in hand dermatitis (Table 10-6).

Efficacy

In an initial non-controlled pilot study, 38 CHD patients were treated with alitretinoin (either 20 mg or 40 mg). 95% of patients clinically improved with therapy, 55% achieving a very good response.⁸⁸

Two randomized, double-blind, placebo controlled studies were performed by Ruzicka et al.^{89,90} with oral alitretinoin. In the first study, 319 patients with refractory moderate-to-severe hand dermatitis were randomized to receive either alitretinoin at doses of 10 mg/day, 20 mg/day, or 40 mg/day, or placebo for 12 weeks. Alitretinoin led to a significant and dose-dependent improvement in all types and severities of chronic hand dermatitis ($p<0.001$).⁸⁹ The second study assessed alitretinoin at 10 mg or 30 mg daily versus placebo for up to 24 weeks in 1032 patients. Significant dose-dependent improvement was seen, with 48% of the 30 mg/day treatment group achieving clear to almost clear hands compared to 17% for placebo ($p<0.001$).⁹⁰

Adverse Events

The most common adverse events reported were headache or dryness of the mucosa and/or lips; one patient developed erysipelas that required hospitalization. A dose-dependent

increase in triglyceride levels, slightly decreased hemoglobin level, and a decreased free thyroxin level and thyroid-stimulating hormone level were also observed.^{89,90}

Relapse

Relapse rate was calculated at 26%⁸⁹ with an average time to relapse being 5.5-6.2 months in the absence of antidermatitis medications.⁹⁰

OTHER THERAPIES

Botulinum Toxin Injections

Hyperhidrosis is known to be an exacerbating factor in patients with vesicular hand dermatitis. Botulinum toxin is a potent inhibitor of acetylcholine, which is involved in the production and release of sweat from eccrine sweat glands.⁹¹ Two papers assessed using botulinum toxin injections to control symptoms of vesicular hand dermatitis (Table 10-7).

Swartling et al.⁹² performed an open-label study of 10 patients with recurrent vesicular hand dermatitis. Patients received intradermal injections with botulinum toxin in one hand, while the other hand served as the control. Seven out of ten (70%) reported good to very good effects 5-to-6 weeks post-injection; six of the responders had a history of hyperhidrosis.⁹² Wollina and Karamfilov⁹¹ performed a similarly designed study and found significant improvement of dermatitis symptoms in the hand injected with botulinum toxin over control ($p<0.01$). No adverse events were reported.

Iontophoresis

Iontophoresis is the noninvasive transdermal transfer of ions by direct current that has been shown to be effective in treating hyperhydrosis.⁹³ In one open-label study (Table 10-7), 20 patients with recurrent vesicular (dyshidrotic) hand dermatitis were treated with pulsed direct current iontophoresis, which led to a significant improvement in symptoms ($p<0.001$). No adverse effects were reported.⁹³

Ranitidine

Ranitidine is a histamine type-2 receptor antagonist with immunomodulating properties.⁹⁴ After observing improvement in CHD patients who were on ranitidine for gastric ulcers, Veien et al.⁹⁴ randomized 47 patients with chronic atopic hand dermatitis to receive either oral ranitidine 300 mg twice daily or placebo for 16 weeks. Overall, there was a trend toward symptom reduction in patients on ranitidine ($p=0.07$). No side effects were observed (Table 10-7).

TABLE 10-7—Selected* Studies of Botulinum Toxin, Iontophoresis, and Ranitidine for Hand Dermatitis

Lead Author, Date	Study Type	Treatment	Dose	Treatment Duration	Hand Dermatitis Type	N	Efficacy	Adverse Events Related to Treatment	Relapse
Wollina, 2002 ³¹	Open, L/R controlled	Intradermal botulinum A injection vs. control	100 units of botulinum toxin A diluted in 2 mL physiologic sodium chloride solution were injected intradermally in 0.1mL aliquots.	1 series of injections; patients then followed for 8 weeks	Vesicular Hand Dermatitis	8	Treated hands showed significant improvement over control ($p<0.01$)	—	—
Swartling, 2002 ³²	Open, L/R controlled	Intradermal botulinum A injection (Botox) vs. control	2 units of Botox injected intradermally every 15 mm on the palm.	1 series of injections; patients then followed for 5-6 weeks	Vesicular Hand Dermatitis	10	Self-assessment showed good to very good effect in 7/10 (70%); disease activity scores decreased by 54% with treatment vs 29% with control.	—	—
Odia, 1996 ³³	Open, randomized, L/R controlled	Tap water iontophoresis	Pulse directed current: 9V, 9.8 kHz high-frequency phase direct current; Direct current: 18V ripple voltage. Amperage varied according to individual skin resistance, but this variation was small.	3 weeks	Vesicular Hand Dermatitis	20	Total severity significantly improved with treatment ($p<0.001$).	—	—
Veien, 1995 ³⁴	Double-blind, randomized, placebo-controlled	Oral ranitidine vs. control	300 mg BID	16 weeks	AD	47	Trend towards symptom reduction with treatment ($p=0.07$).	—	—

*Please refer to methods in main text regarding search criteria and how papers were selected.
CHD=chronic hand dermatitis; ACD-allergic contact dermatitis; ICD-irritant contact dermatitis; AD-atopic dermatitis

DISCUSSION

Lifestyle changes are vital for the treatment of hand dermatitis (Figure 10-8). However, lifestyle changes alone often fail to control chronic disease, and medical interventions are frequently necessary. Medical therapy is generally initiated in a step-wise fashion: first-line therapy includes treatment with topical steroids, topical immune modulators, or topical retinoids. Second-line therapy comprises phototherapy, ionizing radiation, or systemic therapy with oral steroids, oral retinoids, methotrexate, cyclosporine, or other systemic immunomodulators or antimetabolites.⁴²

TOPICAL AGENTS

Topical Steroids

Topical steroids are the mainstay of hand dermatitis treatment; however, there are no standard recommendations available as to how they should be used. The studies that met the search criteria showed that corticosteroid creams of various strengths were equally efficacious in treating hand dermatitis.^{47,48} The choice of corticosteroid can thus be guided by the drug's side effect profile, cost, as well as the severity and chronicity of the dermatitis. Intermittent-long-term use of high potency topical steroids may help control symptoms of chronic hand-dermatitis with minimal side effects.^{46,50} Adding zinc sulphate may additionally help to decrease symptoms and recurrence rates.⁴⁹ Warshaw³¹ states that in general, ointments are more effective than creams and contain fewer preservatives. In her opinion, generic triamcinolone ointment 0.1% in a petroleum base is the preferred topical ointment.³¹ Both the 'soak and smear' technique, where patients soak hands in water for 20 minutes prior to applying a topical steroid, and using occlusion to enhance drug delivery, can improve clearance rates.^{25,30,95}

Local adverse reactions with topical corticosteroids are common and include: epidermal and dermal atrophy, striae, and purpura.⁹⁶ Absorption of the steroid can lead to systemic complications, such as: suppression of the hypothalamic-pituitary-adrenal axis, Cushing's syndrome, osteoporosis, and hyperglycemia, or diabetes.⁹⁶ These adverse effects limit corticosteroid use for long-term treatment. High-potency topical steroids, especially when used for a long duration, over a large portion of the body, or with occlusion, increase the risk of systemic effects.⁹⁶ Although rare, corticosteroids may also act as contact allergens. Consider this when topical therapy fails to relieve a dermatitis.⁹⁷

Topical Immunomodulators

Topical immunomodulators tacrolimus (FK 506) and pimecrolimus (SDZ ASM 981) work by inhibiting the release of inflammatory cytokines from T lymphocytes and mast

cells, thus down-regulating T-cell activity.^{98,99} When applied topically, the systemic absorption of both tacrolimus and pimecrolimus is low.^{53,100} The most commonly reported adverse events are burning and pruritus at the application site.^{51,53} Additionally, unlike topical steroids, neither tacrolimus nor pimecrolimus induce skin atrophy.^{98,101} The studies of this search generally found that tacrolimus and pimecrolimus are effective for all symptoms of chronic hand dermatitis, except for vesicularization.^{52,54} Due to their low systemic absorption and favorable side effect profiles, tacrolimus and pimecrolimus can be effective steroid-sparing agents, useful when lengthy treatment is necessary.

Topical Retinoids

Retinoids activate the retinoid X (RXR) nuclear receptor, which then in turn activates a cascade of other receptors that collectively affect skin physiology.⁵⁷ Bexarotene has been used in the treatment of cutaneous T-cell lymphoma since 1999 in the United States.⁵⁷ Hanifin et al.⁵⁷ demonstrated that bexarotene gel can be effective and safe for use in hand dermatitis as well. Adverse events, such as stinging and burning at the application sites can be minimized if the gel is confined only to the areas of dermatitis.⁵⁷

IONIZING RADIATION

Ionizing radiation, both superficial x-ray therapy and Grenz ray therapy, has been used for the treatment of dermatoses in dermatology for more than 50 years. Two studies in this search,^{58,60} found that superficial radiotherapy led to significant improvement in the symptoms of hand dermatitis, comparable to that of PUVA.⁶⁰ However, one study failed to find superficial radiotherapy to be superior to placebo in the long term.⁵⁹ Regarding adverse effects related to superficial radiation therapy, Rowell¹⁰² performed a follow-up study of 100 patients treated with 1500-1600 rad of superficial radiotherapy for various dermatoses and found that four had developed basal cell carcinoma and one had developed squamous cell carcinoma. It is therefore recommended that no more than 1200 rad of therapy is given to an area of skin over a patient's lifetime.¹⁰²

Grenz rays, also called ultra-soft x-rays or Bucky rays, are x-rays with a longer wave length such that most of the energy is absorbed in the epidermis or upper layers of the dermis.¹⁰³ Grenz rays are associated with fewer cases of radiodermatitis than x-rays, but can cause skin hyperpigmentation or hypopigmentation, atrophy, and telangiectasias.¹⁰³ An association with cancer cannot be ruled out.¹⁰³ Data regarding the efficacy of Grenz rays for use in hand dermatitis is conflicted: one paper shows that Grenz ray therapy leads to significant therapeutic improvement,⁶² while another fails to show the therapy to be superior to placebo.⁶¹ One case report by Walling et al.¹⁶ describes the use of Grenz ray therapy in a 48-year-old man with recalcitrant frictional hyperkeratotic hand dermatitis. After six

sessions, the dermatitis cleared completely without recurrence. However, Farris et al.⁶³ compared conventional superficial x-rays to Grenz rays and found treatment with superficial x-rays led to significantly better outcomes. A common dosing regimen for the treatment of hand dermatitis is 300 rad (3 Gy) given every 1 to 3 weeks for up to six sessions.^{61–63} This is generally followed by a 6 month treatment-free interval.³¹

Duff et al.⁶⁴ assessed megavoltage radiation therapy in the treatment of hand dermatitis, and found six of the nine patients improved with treatment, with only 20% relapsing. Adverse effects were not reported, but megavoltage radiation to an extremity can cause subcutaneous fibrosis, joint stiffness, and edema after treatment.⁶⁴ Duff et al.⁶⁴ used maximum dose of 1200 cGy dose to treat hand dermatitis. Skin, lymphatics, vasculature, and adult cartilage and bone have been safely irradiated with doses greater than 5000 cGy, although cases of radiation-induced cancer do exist.⁶⁴

PHOTOTHERAPY

Phototherapy is the most studied treatment for hand dermatitis. UVA-1, Psoralen and UVA-1 (PUVA), and UVB have all been used and shown to be effective. No one treatment has proven to be vastly superior, although one paper suggests PUVA may lead to better outcomes than UVB.⁷⁸ Phototherapy treatment, therefore, may be driven by availability and side-effect profiles.

UVA-1 irradiated skin histologically demonstrates a reduction in mast cells and an induction in collagenase activity.⁶⁵ Long-term effects of this treatment therapy are not well known, and therefore, it is recommended that patients not be treated more than twice yearly with 15 irradiations per treatment cycle, be at least 18 years of age, and regularly monitored for adverse skin sequelae, such as skin cancer.⁶⁵

The addition of psoralen, a photosensitizer, to UVA therapy is advantageous because less UVA dose is needed in order to achieve an effect.¹⁰⁴ Although the mechanism of action for PUVA in the treatment of hand dermatitis is not well understood, the impairment of DNA synthesis in peripheral blood lymphocytes and inactivation of Langerhans cells may play a role.⁶⁹ Additionally, PUVA is known to thicken the stratum corneum, which can protect from irritant and allergen exposure.⁶⁹ Psoralen can be administered either topically or orally when used in combination with UVA, and both routes of administration are effective in the treatment of hand dermatitis.^{75,76} Topical PUVA utilizes either 8-methoxysoralen (8-MOP) or 5-methoxysoralen (5-MOP). These can be applied either by painting on an ointment, cream, emulsion, or gel ('paint' PUVA), or soaking the hands in a solution of diluted psoralen photosensitizers ('bath' PUVA).¹⁰⁴ Hand dermatitis patients respond well to both bath-PUVA and paint-PUVA modalities.⁷⁴ Additionally, 8-MOP and 5-MOP have similar efficacy, but 5-MOP is associated with greater

phototoxicity and pigmentary changes.¹⁰⁴ To avoid phototoxic side effects with PUVA (topical 1% psoralen), such as painful erythema and pruritus, the recommended starting dose is 0.25 J/cm² with subsequent incremental increases of 0.25 J/cm²; therapy should be given no more than three times per week.¹⁰⁵ Topical PUVA is more favorable than oral PUVA because it avoids systemic adverse effects such as nausea, vomiting, generalized sunburn, photoaging, and elevated liver transaminases. Bath PUVA allows a more uniform absorption of the photosensitizer into the skin,^{65,104} but paint PUVA allows the photosensitizer to be limited only to diseased areas.⁷⁴ Photosensitivity is lost more rapidly with topical PUVA than oral PUVA, meaning prolonged protection of the skin and eyes is not necessary, and ocular photo-damage can be avoided.⁶⁵ Topical PUVA is preferable to oral PUVA in patients with hepatic dysfunction, gastrointestinal issues, cataracts, and when shorter irradiation times are needed or drug interactions are anticipated, as with patients receiving anticoagulation.^{104,106} Multiple treatments with oral PUVA are associated with an eleven to thirteen-fold increased risk for basal cell carcinomas and three to seven-fold increased risk for squamous cell carcinomas. There is insufficient evidence to conclude that topical PUVA would decrease the risk of carcinogenesis.¹⁰⁴

Narrowband UVB (311-312 nm) has greatly replaced broadband UVB as it has been found that these wavelengths improve therapeutic results.¹⁰⁷ Acute adverse effects associated with UVB therapy are erythema and burning, local blisters, folliculitis, and pruritus; long-term effects include photoaging and carcinogenesis.¹⁰⁶ Two studies revealed less risk adverse events with UVB therapy than PUVA.^{77,78}

One major downfall of phototherapy is the inconvenience of having to take time to go to a center and receive treatments. Therefore, home phototherapy units, which have been shown to be as effective in the treatment of hand dermatitis as clinic or hospital units, may be beneficial.^{76,84}

SYSTEMIC THERAPIES

Oral Corticosteroids

No studies could be found that evaluated oral steroids specifically for use in hand dermatitis. Despite this, they remain important in treatment and should be considered when rapid control is needed.⁴² Warshaw et al.¹⁴ comment in their hand dermatitis review that "short bursts of prednisone at 60 mg as a single dose in the morning for 3 to 4 days and repeated every 2 to 4 months as needed have been helpful." Although oral steroids can considerably improve patients' symptoms, side effects limit their use. These side effects can range from mild to life-threatening. Acutely, they include skin atrophy, striae, and telangiectasias; hypertension; hyperglycemia; pancreatitis; and

hematologic, immunologic, and neuropsychotic effects.¹⁰⁸ Chronic use can lead to osteoporosis, aseptic joint necrosis, hypothalamic-pituitary-adrenal axis insufficiency, glaucoma, hyperlipidemia, growth suppression, gastrointestinal and hepatic effects, and possibly congenital malformations.¹⁰⁸

Cyclosporine

Cyclosporine is an immunosuppressant drug and potent T-cell inhibitor that acts by interrupting intracellular transduction pathways in lymphocytes.¹⁰⁹ Nephrotoxicity, hypertension, and carcinogenesis are adverse effects associated with cyclosporine use. Cyclosporine is eliminated by hepatic metabolism. The recommended starting dose is 2.5 mg/kg/day, and if improvement is not noted, the dose may be increased in increments of 0.5 to 1.0 mg/kg/day, until a maximum of 5 mg/kg/day is reached.¹⁰⁹

Cyclosporine is as effective as topical steroids in the treatment of hand dermatitis and can be used if initial topical treatments fail to improve symptoms.⁸⁶ Although the study found in the literature search reported that 50% of patients treated with cyclosporine relapsed,⁸⁶ long-term remission is possible with cyclosporine treatment. A study by Granlund et al.¹¹⁰ evaluated the long-term efficacy of cyclosporine in 27 patients with CHD and found that 1 year after completing therapy, 78% were still in remission.

Methotrexate

Methotrexate is a synthetic analog to folic acid that irreversibly inhibits dihydrofolate reductase and is cytotoxic.¹⁰⁹ Nausea, vomiting, and diarrhea are the most common major side effects. Major toxicities include: hepatotoxicity, bone marrow suppression, and carcinogenesis; it is an abortifacient and teratogen.¹⁰⁹ Methotrexate can be taken either orally or injected. It is eliminated by renal excretion.¹⁰⁹ Common doses are 7.5 to 25 mg/week.¹⁰⁹ Methotrexate has long been used in other dermatoses, one case series reports that low doses are effective in resolving recalcitrant hand dermatitis.⁸⁷

Oral Retinoids

Alitretinoin is an endogenous retinoid and pan-agonist of the retinoid receptor, binding to both retinoic acid receptors and retinoid X receptors.¹¹¹ Retinoids are known to affect cell proliferation, differentiation, and apoptosis.¹¹¹ Although the exact mechanism of alitretinoin's connection with hand dermatitis is not well understood, it has been shown in mice to have immunomodulating and anti-inflammatory effects, as well as the ability to downregulate keratinocytes and dermal endothelial cells.¹¹¹ Alitretinoin is metabolized by the cytochrome P450 system of the liver and is mainly excreted in the urine.¹¹¹ Overall, alitretinoin

is well tolerated, with headache being the most common adverse event.^{89,90} Abnormal laboratory test results, such as low thyroid-stimulating hormone levels, and high cholesterol and triglyceride levels, appear to be dose dependent, and may be reversible if the dose is reduced.¹¹¹ Doses used in the treatment of CHD are 10-30 mg daily, although the 30 mg dose may be preferable since efficacy is dose dependent.⁹⁰ Treatment lasts 12-24 weeks, depending on the response.^{90,111} Women of child-bearing age must undergo pregnancy testing, and pregnancy is an absolute contraindication to alitretinoin use as the drug is teratogenic.¹¹¹ Other contraindications include hepatic or severe renal insufficiency and breast-feeding.¹¹¹ Alitretinoin should not be given with tetracyclines because of reports of benign intracranial hypertension occurring with concomitant use.¹¹¹ Overall, oral alitretinoin can produce clinical responses in patients with moderate-to-severe hand dermatitis that have failed other therapies. It is generally well tolerated, but attention should be paid to fasting lipid levels and thyroid hormones.

OTHER THERAPIES

Botulinum Toxin & Iontophoresis

Both botulinum toxin injections and iontophoresis have been shown to improve the symptoms of chronic vesicular hand dermatitis by controlling hyperhidrosis, a common exacerbating factor.

Botulinum toxin, from the gram-positive bacillus *Clostridium botulinum*, is the most poisonous substance known.¹¹² Regarding hyperhidrosis, the toxin blocks the presynaptic release of acetylcholine and causes denervation of sweat glands, leading to a long-lasting inhibition of sweating (approximately seven months).¹¹² Injections of botulinum toxin A are given intradermally and are preceded by some form of analgesia or sedation to reduce pain.¹¹² Adverse events include potential toxin spread into nearby neuromuscular junctions, leading to intrinsic hand muscle weakness.¹¹² Despite this risk, botulinum toxin injections provide significant improvement to patients with hand dermatitis exacerbated by hyperhidrosis.^{91,92}

Iontophoresis has been studied for more than a century and uses a continuous low-voltage current to provide an electrical driving force to transport ions or charged drugs across the stratum corneum, without changing the skin barrier itself.¹¹³ Tap water iontophoresis is used to treat hyperhidrosis and is thought to improve symptoms by post-synaptically inhibiting sweat gland secretions.⁹³ Commercial iontophoresis devices are available for home use.¹¹² Treatment regimens have patients increasing the amperage to the maximum tolerated, and then treating each site for 30 minutes, twice daily, for up to 2 weeks.¹¹² Adverse effects include pain and small skin burns.¹¹²

Ranitidine

Ranitidine is a histamine type-2 receptor antagonist, commonly used to suppress acid production in the treatment of peptic ulcer disease and gastroesophageal reflux disease.¹¹⁴ Ranitidine is associated with a low incidence of adverse effects; headache, tiredness, and gastrointestinal disturbances are most common.¹¹⁵ A few case reports have described cases of anaphylaxis to ranitidine.¹¹⁴ An initial study by Veien et al.⁹⁴ showed a trend towards symptom reduction in patients with atopic hand dermatitis with treatment, but more studies are needed.

ADDITIONAL THERAPIES

Other treatments that have been shown in case reports to be effective for recalcitrant chronic hand dermatitis include mycophenolate mofetil,¹¹⁶ alefacept,¹¹⁷ and vitamin E.¹¹⁸ (It should be noted, though, that there is one report in the literature where mycophenolate mofetil induced a case of acute vesicular hand dermatitis.¹¹⁹) Additionally, azathioprine has been shown to be effective in the treatment of

atopic dermatitis and may prove to be helpful in the treatment of hand dermatitis as well.¹²⁰

CONCLUSION

Hand dermatitis is a common disease, especially prevalent in people who participate in ‘wet-work’. The disease often has a relapsing-and-remitting course that is chronic, debilitating, and frustrating. The etiologies and clinical manifestations of the disease are numerous, and no universally accepted guidelines are available for the classification, diagnosis, and treatment of hand dermatitis. Lifestyle factors, including the avoidance of any identified irritants, allergens, and exacerbating factors, along with the aggressive use of emollients and topical steroids are the mainstay of treatment and can be effective in mild or acute cases. In cases where hand dermatitis becomes chronic, though, additional interventions are necessary, and no one intervention has proven to be vastly superior to the others. Since there are few well-designed studies to guide clinical practice for the treatment of hand dermatitis, more randomized controlled trials are needed that adhere to modern quality criteria.

What We Know

- Hand dermatitis prevalence ~ 10%, incidence ~ 8%, although this is increased in certain populations, especially those associated with ‘wet-work’.
- Hand dermatitis affects all age groups.
- Etiology is multifactorial but frequently involves disruption of the normal skin barrier.
- ICD is direct skin damage caused by irritants and can occur in anyone. ACD is the result of a type IV immune reaction because of contact with an allergen to which a person has been previously sensitized. AD is an inherited endogenous dermatitis.
- Morphologies of hand dermatitis vary based on etiology, chronicity, and severity.
- Diagnosis involves a thorough history, physical examination, and patch testing.
- Lifestyle modifications involving avoiding known irritant/allergens, protecting hands while performing wet-work, and using emollients aggressively are essential in treatment.
- Group I-V topical steroids can improve symptoms of hand dermatitis with similar efficacy. Adding zinc sulphate may augment the effects. Side effects, such as skin atrophy, striae, and telangiectasias, limit long-term use. Intermittent use may help prevent relapse.
- Topical tacrolimus and pimecrolimus are of use in reducing all symptoms of hand dermatitis except vesicles. Skin side-effects are mild. Tacrolimus alone may not effectively prevent relapses.
- Topical bexarotene gel leads to durable responses with minimal side effects.
- UVA-1, Psoralen and UVA-1 (PUVA), and UVB have all been used and shown to be effective, with no one treatment proven to be superior. In general, bath PUVA has fewer side effects than oral PUVA is more practical for the treatment of hand dermatitis.
- Ionizing radiation treatments may prove to be helpful in patients that have failed other therapies.
- Cyclosporine can significantly reduce symptoms of hand dermatitis, but relapse rates are generally high.
- The oral retinoid, alitretinoin, can lead to a significant and dose-dependent improvement in all types and severities of chronic hand dermatitis with generally mild side effects and low relapse rates.
- Methotrexate cleared symptoms in five patients, but more randomized controlled trials are needed.
- Vesicular hand dermatitis exacerbated by hyperhidrosis may benefit from intradermal botulinum toxin injections or tap water iontophoresis.
- Few well-designed studies to guide clinical practice for the treatment of hand dermatitis, and more randomized controlled trials are needed that adhere to modern quality criteria.

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Treatment of Acute Urticaria and Angioedema

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Urticaria was first documented by the Chinese in the 10th century BCE and it was named as “Feng Yin Zheng”.¹ William Cullen was probably the first to use the term “urticaria” in 1769.² It was recognized as a distinct nosological entity by Hippocrates.

Urticaria commonly known as hives is a cutaneous syndrome characterized by upper dermal edema (wheal) and erythema (flare) that blanches on pressure.

Essentially, urticaria corresponds to the activation of dermal mast cells. Mast cell activation induces inflammatory reactions by secreting chemical mediators stored in pre-formed granules (histamine, tryptase, or chymotrypsin) and by synthesizing and secreting leukotrienes, prostaglandins, chemokines, and cytokines.³

Acute urticaria may be accompanied by angioedema. Angioedema is defined as rapid edema involving the dermis, subcutaneous tissue,¹ mucosa, and submucosal tissue. Acute urticaria is usually pruritic. It completely resolves within 6 weeks but mostly lasts less than 2 days.¹ The epidermis is generally unscathed, and scratch marks are relatively uncommon despite the severe itching of urticaria. Thus, desquamation does not occur in urticaria or angioedema. Although pruritus is the main symptom of the disease, pain and tenderness can occasionally occur. Further, acute urticaria is more common in children than in adults.⁴ Urticaria usually becomes evident a few minutes after exposure to the trigger. As acute urticaria lasts for a short period and, in many cases, is not severe, it often does not come to the attention of dermatologists or allergologists. However, angioedema without urticaria should raise suspicion of a hereditary form of angioedema (particularly complement [C]-1-inhibitor deficiency (C1-INH)), which can be often more severe with laryngeal involvement.

As acute urticaria lasts for a short period of time and in many cases may not be severe, it often does not come to the attention of dermatologists or allergologists.

ETIOLOGY

Urticaria may be caused by a state of hypersensitivity to foods or drugs, foci of infection, physical agents (heat, cold, light, friction), or psychological stimuli.³ The majority of drugs available today are capable of causing acute

urticaria. Angioedema, on the other hand, can be hereditary or acquired. The hereditary form has three subtypes as follows. Type I is characterized by low plasma levels of normal C1 esterase inhibitor protein. Type II patients are antigenically intact, and this type is defined by the presence of normal or elevated levels of dysfunctional C1-esterase inhibitor. Type III has been identified as a new subtype of angioedema that occurs mainly in women with normal functional and quantitative complement levels and does not have any specific laboratory marker. Some type III patients are characterized by X-linked dominant inheritance. Both estrogen-dependent and estrogen-independent forms have been recognized in hereditary angioedema type III;⁵ these may be caused by mutations in the factor XII gene.^{6,7} Non-hereditary angioedema is the most common form of angioedema and can be caused by different triggers mainly via an immunologic response. ACE inhibitor- and NSAID-induced angioedemas comprise the most common drug-induced angioedemas.⁴ Table-1 summarizes all the known causes of acute urticaria and angioedema.

EPIDEMIOLOGY

The published reports on the prevalence of urticaria differ widely. The available literature shows that 0.05–23.2% of the general population experience urticaria in their lifetime. Gaig et al. reported a cumulative incidence of 18.72% for acute urticaria in the Spanish population.⁸ There is no doubt that urticaria and angioedema affects women more than men.^{8–14} Acute urticaria tends to affect younger individuals, while chronic urticaria is typically a disease affecting middle-aged individuals. The coexistence of acute urticaria and angioedema is more frequent in younger patients.^{15,16}

METHODS

Pubmed, Scopus, and ISI Web of Science were searched to find published randomized-controlled trials (RCT) of treatments for acute urticaria and/or acute attacks of hereditary or nonhereditary angioedema. References of selected papers were reviewed to find any other relevant study.

TABLE 11-1—Etiologic Factors for Urticaria/Angioedema

Etiologic factor	Examples	Etiologic factor	Examples
Food and food additives	<ul style="list-style-type: none"> • Saccharine • Asparagus, cow's milk protein, nuts, fish, chocolate, fruits (berries), eggs, peanut, tomatoes, shellfish • Sodium disulfite • Sodium benzoate 	Lymphoproliferative disorders	<ul style="list-style-type: none"> • B cell type (Main cause of acquired angioedema)
Medications	<ul style="list-style-type: none"> • Biologicals (Infliximab) • Antibiotics: beta lactams (penicillins, ampicillin, amoxicillin, cephalosporins), aminoglycosides, Sorbitol complexes • Tetracyclines, roxithromycin, sulphonamides • Nonsteroidal anti-inflammatory agents: piroxicam, aspirin, other salicylates • Enzymes: streptokinase, trypsin, chymopapain • Antifungal agents: fluconazole, ketoconazole • Steroids • Angiotensin-converting enzyme inhibitors • Theophylline • Hormones: insulin, corticotrophin, vasopressin • Radiographic contrast media • Tetrazine • Hydralazine • Hyoscine butylbromide • Narcotic analgesics • Bupropion • Quinidine • Cimetidine • Tripelennamine • Opiates • Anesthetic agents (local and general) • Anticancer drugs • Muscle myorelaxants (curare) • Alcohol • Vaccines • Dextrans • Vitamins • Hyaluronidase • Mannitol • Protamine • Eugenol • Blood transfusions 	Toxicity	<ul style="list-style-type: none"> • Insect bites/venom (bee, ant, flea) • Plants (Grevillea juniperina) • Sea animals
Contact urticaria allergens	<ul style="list-style-type: none"> • Nickel 	Physiological changes	<ul style="list-style-type: none"> • Menstruation, pregnancy • Anxiety, stress
		Parasitic infection	<ul style="list-style-type: none"> • Dicrocoelium dendriticum infestation • Anisakis simplex • Blastocystis • Schistosomiasis • Giardiasis • Pigeon tick (<i>Argas reflexus</i>) • Toxoplasmosis • Malaria
		Viral infections (the most common)	<ul style="list-style-type: none"> • Hepatitis A • Hepatitis B • Infectious mononucleosis • Parvovirus B19 • <i>Haemophilus influenzae</i> b
		Bacterial infection	<ul style="list-style-type: none"> • <i>Mycoplasma pneumonia</i> • <i>Streptococcal</i> infection • <i>Shigellosis</i> • <i>Ehrlichiosis</i> • <i>Brevibacterium iodonium</i> • <i>Yersinia enterocolitica</i> • <i>Helicobacter pylori</i>
		Fungal infection	<ul style="list-style-type: none"> • <i>Aspergillus</i>
		Hormonal disorders	<ul style="list-style-type: none"> • Decrease in TSH
		Neoplasm	<ul style="list-style-type: none"> • Acute myeloid leukemia • Acute lymphoblastic leukemia
		Physical stimuli	<ul style="list-style-type: none"> • Mechanical: dermatographism, pressure, vibration • Thermic: heat, cold • Cholinergic: sweat • X ray
		Enzyme deficiency	<ul style="list-style-type: none"> • C1 inhibitors deficiency: hereditary, acquired
		Mastocytosis	<ul style="list-style-type: none"> • Cutaneous and systemic
		Autoimmune disorders	<ul style="list-style-type: none"> • Urticaria vasculitis • Systemic lupus erythematosus • Cryoglobulinemia • Wissler-Fanconi syndrome
		Autoimmune idiopathic	<ul style="list-style-type: none"> • Antibody to IGE receptor or IGE

THERAPY

Antihistamines

Antihistamines (H1 or H2 receptor blockers) remain the therapy of choice for acute urticaria. H1 receptor antagonists are mainly used; these include first (e.g., diphenhydramine)

and second generations (e.g., loratadine, and cetirizine) of the drug. Second-generation H1 antihistamines are less toxic. H2 receptor blockers (e.g., ranitidine, cimetidine, and famotidine) are a class of drugs used to block the action of histamine, especially on parietal cells in the stomach, decreasing the production of acid by these cells.

Is cimetidine or Famotidine more effective than diphenhydramine in the treatment of acute urticaria?

Cimetidine

Efficacy and Safety

In a small trial, the effects of intravenous administration of cimetidine 300 mg and diphenhydramine 50 mg in acute urticaria were compared with each other. Although cimetidine relieved urticaria more than diphenhydramine (80% vs. 45%), there was no significant difference between the two drugs.¹⁷ In another RCT, cimetidine, 300 mg and diphenhydramine, 50 mg were compared as intramuscular treatments. Cimetidine was comparable but not superior to diphenhydramine. The sedation level was significantly higher in the diphenhydramine-treated patients.

Comments and Limitations

There is no randomized placebo-controlled trial to prove the efficacy of either cimetidine or diphenhydramine. Cimetidine is comparable to diphenhydramine.

Famotidine

Efficacy and Safety

In an RCT, two intramuscular injections of 20 mg famotidine did not change the intensity of urticaria and pruritus more than single dose intramuscular administration of 50 mg diphenhydramine (Table 11-2).¹⁸ No major side effect was mentioned. No significant difference between famotidine and diphenhydramine was noted in terms of sedation.¹⁸

Comments and Limitations

Famotidine is as effective as diphenhydramine. The efficacy of neither drug has been confirmed by placebo-controlled trials yet.

Is addition of cimetidine to diphenhydramine beneficial in the treatment of acute urticaria?

Efficacy and Safety

Runge et al.¹⁷ compared cimetidine 300 mg plus diphenhydramine 50 mg intravenously with diphenhydramine 50 mg plus placebo intravenously. Eleven out of twelve patients (91.6%) vs. 5/11 (45.4%) obtained relief from urticaria, respectively. Side effects included burning sensation

at the injection site in one patient per group in addition to lightheadedness and nausea in three patients treated with cimetidine plus diphenhydramine. Lin et al.¹⁹ investigated the additive effects of intravenous ranitidine 50 mg to intravenous diphenhydramine 50 mg. Acute urticaria persisted after 2 h in 4/29 (13.8%) of patients in the combination therapy group vs. 11/24 (45.8%) in diphenhydramine group. In a similar randomized trial, Knight et al. compared the efficacy of intravenous ranitidine 50 mg plus diphenhydramine 50 mg versus diphenhydramine alone. The addition of ranitidine relieved acute urticaria in 44/49 (89.8%) of patients after 2 h, while diphenhydramine alleviated urticaria in 33/43 (76.7%) of patients. In both trials, there was a mild decrease in the heart rate, particularly in the combination treatment group patients. No bradycardia was reported in any of these trials.

Comments and Limitations

Ranitidine and cimetidine may have some additive effects to diphenhydramine in the treatment of acute urticaria or other acute allergic reactions.

Can cetirizine prevent acute urticaria formation in atopic dermatitis patients?

Cetirizine is the active carboxylated metabolite of the first-generation antihistamine, hydroxyzine. It is a potent H1 blocker in addition to its anti-inflammatory properties, which include the inhibition of eosinophil chemotaxis.²⁰

Efficacy and Safety

In the only preventive trial involving cetirizine for preventing acute urticaria in atopic dermatitis patients, oral cetirizine (0.5 mg/kg/day) was compared to placebo administration. Acute urticaria occurred in 5.6% of cetirizine-treated patients and in 15.7% of placebo-treated patients after 18 months. Such a significant difference was not noted at an earlier time point (6 months). Moreover, patients under cetirizine therapy suffered a lower number of episodes during the 18-month therapy period. No side effects were reported in this RCT.²¹

Comments and Limitations

Second-generation H1 antihistamines such as cetirizine may be considered effective prophylactic agents.

Corticosteroids

Short-term oral corticosteroid therapy has been considered as an alternative for severe acute urticaria.

TABLE 11-2—Summary of Published Studies on Acute Urticaria Treatments

Study	Treatments	No. of patients	Efficacy	Safety	Notes
Runge et al., 1992 ¹⁷	Cimetidine 300 mg plus placebo IV vs. DPH 50 mg plus placebo IV vs. combined	10 vs. 11 vs. 12	Urticaria relief: 8/10 (80%) vs. 5/11 (45.4%) vs. 11/12 (91.6%), p<0.05 for DPH vs. combination therapy; Treatment failure: 3/10 (30%) vs. 4/11 (36.3%) vs. 2/12 (16.6%), p>0.05	Burning sensation in IV injection site: 0/10 (0%) vs. 1/11 (9%) vs. 1/12 (8.3%); superficial thrombophlebitis: 2/10 (20%) vs. 0/11 (0%) vs. 0/12 (0%); lightheadedness or dizziness: 2/10 (20%) vs. 0/11 (0%) vs. 2/12 (16.6%); nausea and chills: 0/10 (0%) vs. 0/11 (0%) vs. 1/12 (8.3%), p>0.05 for all	Short follow-up (30 minutes)
Moscati and Moore, 1990 ⁴³	300 mg cimetidine IM vs. 50 mg DPH IM	46 vs. 47	Overall improvement: 2.870 ± 0.341 vs. 2.723 ± 0.452 (p>0.05); Itching: –1.174 ± 0.996 vs. –1.489 ± 1.019 (p>0.05); Wheal intensity: –0.935 ± 0.646 vs. –0.915 ± 0.654, p>0.05	Sedation (change from baseline): 0.37 ± 0.61 vs. 1.085 ± 0.855, p<0.0001	Short follow-up (30 minutes)
Knight et al., 1999	50 mg ranitidine IV plus 50 mg DPH IV vs. placebo plus 50 mg DPH IV	49 vs. 43	Urticaria (hour 2): 5/49 (10.2%) vs. 10/43 (23.2%), p<0.05	Heart rate: 85 vs 86 (baseline), 76 vs. 82 (hour 1) (p=?), 75.6 vs. 79 (hour 2) (p=?)	Abstract only, significances of safety comparisons are not clear.
Lin et al., 2000 ¹⁹	50 mg ranitidine IV plus 50 mg DPH IV vs. placebo plus 50 mg DPH IV	29 vs. 24	Urticaria (hour 2): 4/29 (13.8%) vs. 11/24 (45.8%), p<0.05	Heart rate: 86.0 vs. 86.0 (baseline), 76 vs. 82 (1 hour) (p=?), 76 vs. 80 (2 hour) (p=?)	Both acute urticaria and angioedema patients were included. Significances of safety comparisons are not clear.
Watson et al., 2000 ¹⁸	Two doses of 20 mg famotidine IM vs. 50 mg DPH IM	15 vs. 10	Change in pruritus (VAS): 36 mm vs. 54 mm, p>0.05; Intensity of urticaria (VAS): 34 mm vs. 34 mm, p>0.05; Change in body surface area involved: 20% vs. 8%, p>0.05	Change in sedation (VAS): 0 mm vs. 20 mm, p>0.05	Acute urticaria of less than 72 hours duration, Short follow-up (30 minutes)
Pollack and Romano, 1995 ²²	50 mg DPH IM, and 25 mg hydroxyzine orally TDS, plus either prednisone, 20 mg, or placebo orally BD for 4 days	24 vs. 19	Pruritus (0–10 VAS): 1.3 ± 1.3 vs. 4.4 ± 2.2 for 2 days follow-up and 0.0 ± 0.0 vs. 1.6 ± 1.0 for 5 days follow-up, p<0.0001 for both	0/24 (0%) vs. 0/19 (0%) for prednisolone vs. placebo; Occasional sedation with hydroxyzine treatment in both groups p>0.05	Acute urticaria of less than 24 hours duration; drug adherence was evaluated.
Preventive evidence					
Simons et al., 2001 ²¹	0.25 mg/kg cetirizine orally BD for 18 months vs. 0.25 mg/kg placebo orally BD for 18 months	411 vs. 406	Acute urticaria in 18 months post-treatment: 23/411 (5.6%) vs. 64/406 (15.7%), p<0.01 Acute urticaria event in 6 months post-treatment: 12/411 (2.9%) vs. 18/406 (4.4%), p>0.05 Two or more episodes of urticaria 3/411 (0.7%) vs. 18/406 (4.4%), p=0.001	Not reported	Target population was young children with atopic dermatitis.

DPH, diphenhydramine; IV, intravenous; IM, intramuscular; BD, twice daily; TDS, three times a day

*All of included studies in this table were randomized double-blind studies (Level of evidence IB). Intention to treat analyses were calculated wherever possible.

[†]defined as more than 25% improvement in VAS score.

Is addition of Oral prednisone to antihistamines helpful in the treatment of acute urticaria?

Efficacy and Safety

One randomized trial was found. A combination therapy of intramuscular diphenhydramine 50 mg, and oral hydroxyzine 25 mg thrice daily was considered as the control and was compared to the same regimen, plus oral prednisone 20 mg twice daily for 4 days. Mean pruritus scores were significantly lower for the prednisone group (1.3 ± 1.3 vs. 4.4 ± 2.2 for 2-day follow-up and 0.0 ± 0.0 vs. 1.6 ± 1.0 for 5-day follow-up). Four days treatment of 20 mg oral prednisone did not induce any side effects. Occasional sedation has been observed in both groups.²² In a pseudorandomized trial, 3 days treatment with oral prednisone 50 mg/day was more effective than loratadine 10 mg/day (93.8% vs. 65.9%).²³

Comments and limitations

Short term and low dose oral corticosteroid therapy may be helpful as an adjuvant therapy in acute urticaria.

ANGIOEDEMA (ACUTE ATTACKS)

Table 11-3 includes a detailed description of all relevant studies concerning angioedema.

Is C1 esterase inhibitor more effective than placebo in the treatment or prevention of acute hereditary angioedema?

Pasteurized plasma-derived C1-INH concentrate (Berinert®)

Berinert is the first FDA-approved treatment for acute attacks of hereditary angioedema.

Nanofiltered plasma-derived C1-INH (Cinryze®)

Cinryze® is a C1 esterase inhibitor that is used to prevent attacks in teenagers and adults with hereditary angioedema. It is a lipophilized intravenous preparation. During manufacturing, it undergoes an extra step of nanofiltration for eliminating small-size particles, such as small viruses and prions.

Recombinant human C1-INH (Rhucin®)

Recombinant human C1-INH (rhC1-INH) production is induced in the milk of transgenic rabbits. The main pharmacologic difference between plasma-derived and recombinant C1-INH is the seven times shorter half-life of the latter (<3 h vs. >20 h for plasma-derived C1-INH).^{24,25}

Efficacy and Safety

Craig et al. compared the intravenous administration of 10 mg/kg vs. 20 mg/kg Berinert with a placebo in a double-blind randomized trial. Patients receiving the higher dose had faster time to onset of relief (0.5 h vs. 1.2 h) when compared to the placebo group (1.5 h). There was no serious adverse event, and the frequency of side effects was similar to the placebo group.²⁶ Another placebo-controlled trial evaluated the efficacy and safety of human plasma-derived nanofiltered C1-INH (Cinryze). The median time to complete resolution of symptoms was 12.3 h in the Cinryze group vs. 25 h in placebo group. In a randomized prophylaxis phase trial, Zuraw et al. assessed intravenous application of Cinryze (1000 units) every 3 to 4 days; the attack rate, severity of attacks, and total duration of attacks were all significantly lower in the Cinryze-treated patients. The side effects included lightheadedness, pruritus, rash, and fever.²⁷ Two different doses (100 U/kg and 50 U/kg) of intravenous recombinant human C1-INH were compared to placebo administration in two randomized trials performed in USA and Europe.²⁸ The pooled data of these trials showed that recombinant C1-INH (Rhucin) can reduce the time to onset of symptom relief from 495 minutes in the placebo group to 122 minutes in the group treated with Rhucin 50 U/kg and to 66 minutes in the group treated with Rhucin 100 U/kg. The median times to minimal symptoms were 266, 247, and 1210 minutes in the 100 U/kg Rhucin, 50 U/kg Rhucin, and placebo groups, respectively. Treatment-emergent side effects occurred more frequently in the placebo group.

Comments and limitations

Pasteurized plasma-derived C1-INH concentrate is recommended for acute attacks of hereditary angioedema. The recommended Berinert dosage is 20 units (U) per kilogram of body weight. The safety and efficacy of Berinert for prophylactic therapy have not been established. On the other hand, Cinryze has a definitive effect in preventing future attacks and a modest effect in the treatment of acute attacks. Recombinant human C1-INH at doses of 50–100 U/kg is an effective and safe therapy for acute attacks of hereditary angioedema. However, due to the unique carbohydrate additions (glycosylation) to rhC1-INH, there is a possibility that anaphylaxis may occur,²⁹ although no case of anaphylaxis has been reported due to the administration of rhC1-INH thus far.

Is icatibant more effective than placebo in the treatment of acute hereditary angioedema?

Bradykinin plays a key role in edema formation, and angioedema can be induced by elevated bradykinin

TABLE 11-3—Summary of Published Randomized Studies on Angioedema

Study	Treatments	No. of patients*	Efficacy	Safety	Notes
Craig et al., 2009 ²⁶ (I.M.P.A.C.T.1)	20 U/kg vs. 10 U/kg pasteurized C1 esterase inhibitor concentrate IV vs. placebo	43 vs. 40 vs. 42	Time to onset of symptom relief (hours): 3.89 (\pm 8.20) vs. 7.47 (\pm 10.51) vs. 10.27 (\pm 11.48), $p=0.002$; Time to complete resolution of all HAE symptoms including pain (h): 81.84 (\pm 314.34) vs. 216.06 (\pm 494.23) vs. 125.08 (\pm 382.81), $p=0.02$; Patients with worsened intensity of symptoms between 2 and 4 hours: 2 (4.7%) vs. 8 (20.5%) vs. 13 (31.0%), $p=0.001$; Number of vomiting episodes within 4 hours: 0.1 (\pm 0.41) vs. 0.2 (\pm 0.77) vs. 0.8 (\pm 2.59), $p=0.03$	Adverse events: 9/46 (19.6%) vs. 10/39 (25.6%) vs. 18/41 (43.9%); $p<0.05$ for 20 U/kg vs. placebo Drug-related adverse event: 5% (10.9%) vs. 8 p>0.05 for all (20.5%) vs. 8/41 (19.5%). Severe adverse event was zero in all groups.	Only Hereditary angioedema cases were included. I.M.P.A.C.T.2 is an ongoing open label extension of this trial to further investigate this drug.
Zuraw et al., 2010 ^{a,27}	One or two intravenous injections of nanofiltered C1 inhibitor concentrate (1000 U each) vs. placebo	36 vs. 35 (35 vs. 33)	The onset of unequivocal relief (4 hours): 21/35 (60.0%) vs. 14/33 (42.4%), $p=0.06$; Median time to the onset of unequivocal relief (hours): 2 vs. more than 4, $p<0.05$; Median time to complete resolution of symptoms (hours), 12.3 vs. 25, $p<0.05$	Adverse events: 6/36 (16.6%) vs. 7/35 (20.0%), $p>0.05$ Drug related adverse events: 1/36 (rash at the site of injection, 2.8%) vs. 2/35 (5.7%), $p>0.05$	Only hereditary angioedema cases were included.
Zuraw et al., 2010 ^{b,28}	Recombinant human C1-inhibitor 100 U/kg vs. 50 U/kg vs. saline	30 vs. 13 vs. 30 (29 vs. 12 vs. 29)	Median time to onset of symptom relief (minutes): 66 vs. 122 vs. 495, $p<0.05$; Median time to minimal symptoms (minutes): 266 vs. 247 vs. 1210, $p<0.05$	Drug-emergent adverse events: 7/29 (24.1%) vs. 4/12 (33.3%), vs. 14/29 (48.3%), $p>0.05$ for all; Drug related adverse events: 1/29 (3.4%) vs. 0/12 (0%) vs. 3/29 (10.3%)	Pooled results of two randomized trials. Only hereditary angioedema cases were included.
Reidel et al., 2008 and Cicardi 2010 ^{a,44} (FAST 1)	Icatibant 30 mg SC vs. placebo	27 vs. 29	Time to clinically significant relief (hours): 2.5 vs. 4.6, $p>0.05$; Time to onset of relief (hours): 0.8 vs. 16.9, $p<0.05$, Rescue medication needed 6/27 (22%) vs. 14/29 (48%), $p=0.04$; Time to almost complete relief (hours): 8.5 vs. 23.3, $p>0.05$	Adverse events: 12/27 (44.4%) vs. 19/29 (65.5%) Drug-related adverse events: 4/27 (15%) vs. 1/29 (3%)	Only hereditary angioedema cases were included.
Reidel et al., 2008 and Cicardi 2010a ^{34,44} (FAST 2)	Icatibant 30 mg SC vs. oral tranexamic acid 1 g TDS for 2 days	36 vs. 38	Time to clinically significant relief (hours): 2.0 vs. 12.0, $p<0.001$; Time to onset of relief (hours): 0.8 vs. 7.9, $p<0.05$, Rescue medication needed 5/36 vs. 11/38, $p=0.1$; Time to almost complete relief (hours): 10.0 vs. 51.0, $p<0.05$	Averse events: 19/36 (53%) vs. 16/38 (42%); Drug related adverse events: 5/36 (14%) vs. 4/38 (11%), $p>0.05$ for all	Only hereditary angioedema cases were included.
Lin et al., 2000 ¹⁹	50 mg ranitidine IV plus 50 mg DPH IV vs. placebo plus 50 mg DPH IV	22 vs. 27	No angioedema (hour 1): 7/22 (31.8%) vs. 3/27 (11.1%), $p=0.09$ (hour 2): 11/22 (50%) vs. 13/27 (48.1%), $p>0.05$	Heart rate: 86.0 vs. 86.0 (baseline), 76 vs. 82 (hour 1), 76 vs. 80 (hour 2), $p=?$	Both acute urticaria and non-hereditary angioedema patients were included.
Schneider et al., 2007 ⁴⁵ (EDEMA 1 study)	Single dose of 5, 10, 20, or 40 mg/m ² IV ecballantide vs. placebo	10 (each dose) vs. 8 (placebo)	Significant improvement at the primary attack site: 29/40: (72.5%) vs. 2/8 (25%), $p=0.01$; Time to significant improvement (minutes): 75.0 vs. 303.0, $p<0.05$ Symptom improvement: 8/10 (80%) vs. 5/10 (50%) vs. 7/10 (70%) vs. 9/10 (90%) vs. 2/8 (25%). 5 mg/m ² vs. placebo and 20 mg/m ² vs. placebo were significant.	32/41 (78.0%) vs. 7/8 (87.5%), $p>0.05$	Low sample size; Only hereditary cases were included.

Levy et al., 2008 ³⁶ and Cicardi 2010 ^{b,38} (EDEMA3 study)	30 mg SC ecallantide vs. placebo	36 vs. 36	Median treatment outcome score (4 hours): 50 vs. 0, p = 0.004; Median change from baseline in mean symptom complex severity Score: -1.00 (IQR, -1.50 to 0.00) vs. -0.50 (IQR, -1.00 to 0.00), p=0.01; Estimated time to significant improvement (min): 165 vs. 240, p>0.05	Adverse events 20/36 (56%) vs. 12/36 (33%), p>0.05; Drug related adverse events: 4/36 (11%) vs. 5/36 (14%), p>0.05	Only hereditary cases were included.
Levy et al., 2008 ³⁶ (EDEMA4 study)	30 mg SC ecallantide vs. placebo	48 vs. 48	Treatment outcome score (4 hours): 53.0 (95%CI, 39 to 68) vs. 8.0 (95%CI, -12 to 28), p = 0.003; Change from baseline in mean symptom complex severity score (4 hours): -0.8 (95%CI, -1.0 to -0.6) vs. -0.4 (95%CI, -0.6 to -0.1), p = 0.01	Treatment related adverse events: 4/48 (8.3%) vs. 5/48 (10.4%), p>0.05	Only hereditary cases were included.
Preventive evidence					
Munch and Weeke, 1985 ⁴⁰	Oral tranexamic acid 1.5 g vs. placebo three times daily for 3 months.	12 vs. 12	Days with edema: 36/854 (4.2%) vs. 88/403 (21.8%); Days with itching: 45/854 (5.2%) vs. 104/401 (25.9%), p<0.05 for both	Diarrhea: 5/10 vs. 2/10; abdominal discomfort: 6/10 vs. 2/10, p>0.05 for both	Crossover study; Only nonhereditary angioedema patients were included. Patients were allowed to use other medications such as antihistamines during attacks.
Zuraw et al., 2010 ²⁷	Nanofiltered C1 inhibitor concentrate (1000 units in 10 mL sterile water) vs. placebo (10 mL of saline) every 3 to 4 days.	12 vs. 12	Mean attack rates: 6.26 vs. 12.73 (p<0.001); Mean severity score: 1.3±0.85 vs. 1.9±0.36, p<0.001; Total duration of attacks: 2.1±1.13 vs. 3.4±1.39 days, p=0.002	Adverse events: 3/12 (25%) vs. 3/12 (25%), p>0.05	Cross over study; Two 12-week prophylaxis periods; Only hereditary cases were included.
Weiler et al., 2002 ⁴²	Calcium heparin (200 U/kg; maximum of 10,000 units) or matching placebo SC every 12 hours vs. Inhaled saline vs. heparin (200 U/kg) administered slowly over 5 minutes.	Roughly 17 per group (unclear)	Median flare intensities in inhaled heparin, placebo, and injected heparin groups were 9.2, 8.0, and 5.1, respectively: Transformed estimates: -0.12 (injected heparin vs. inhaled heparin), p=0.02, -0.09 (injected heparin vs. placebo), p=0.1, -0.03 (placebo vs. inhaled heparin), p=0.75	The most common adverse events: injection site reactions, headache, upper respiratory tract infections, knee pain or stiffness, sore throat, and bruising of various body parts. The injection treatments had	

DPH, diphenhydramine; IV, intravenous; SC, subcutaneous; TDS, 3 times a day.
All of included studies in this table were randomized double-blind studies (Level of evidence 1B). *The numbers in the parenthesis denote the number of the patients per group who finished the study.

concentrations,³⁰ which can be caused by either increased bradykinin production or reduced bradykinin inactivation. Icatibant (Jerini, Berlin, Germany) is a selective bradykinin type 2 receptor antagonist with a similar structure and affinity to bradykinin itself. It is a synthetic decapeptide (H-d-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-d-Tic-Oic-Arg-OH). It has only been approved in the European Union, and the US Food and Drug Administration (FDA) approval is pending. Icatibant has been shown to antagonize bradykinin effects such as vasodilation, hypotension, reflex tachycardia, tissue plasminogen activator release, and smooth muscle contractions *in vitro*, *in vivo*, and human studies.³¹⁻³³ It can be administered subcutaneously. Its most common adverse events include erythema, swelling, warm sensation, burning, itching, and cutaneous pain.

Efficacy and Safety

“For Angioedema Subcutaneous Treatment” (FAST)-1 and FAST-2 studies are two double-blind, randomized, multicenter trials that have investigated the efficacy of icatibant against acute attacks of hereditary angioedema.³⁴ In the FAST-1 study, patients received either icatibant (single dose, 30 mg subcutaneously) or placebo, while in FAST-2, patients received either icatibant (single dose, 30 mg subcutaneously) or oral tranexamic acid (3 g daily for 2 days). In FAST-1, the time to onset of relief was 0.8 h vs. 16.9 h for icatibant and placebo, respectively; there were no significant differences between the two groups in terms of the primary outcome measure (Time to clinically significant relief) and other outcomes. In FAST-2, the time to onset of symptom relief was 0.8 h versus 7.9 h in the icatibant and tranexamic acid groups, respectively. No serious drug related adverse events were reported in the FAST-1 and FAST-2 trials.³⁵

Comments and limitations

Icatibant is more effective than oral tranexamic acid in treating acute attacks of hereditary angioedema. Cicardi et al. mentioned the non-superior efficacy of icatibant as compared with placebo; however, the early use of rescue medication may have masked the benefit of icatibant in the FAST-1 trial.³⁴

Is addition of ranitidine to diphenhydramine helpful in the treatment of acute non-hereditary angioedema?

Efficacy and Safety

In the only randomized trial for immunologic angioedema, intravenous combination therapy of ranitidine 50 mg plus diphenhydramine 50 mg was compared to diphenhydramine 50 mg alone. There was no angioedema in 11/22 (50%) of patients in the H1 plus H2 blocker group

as compared to 13/27 (48.1%) patients in the H1 blocker group. Combination therapy decreased the heart rate largely than did treatment with the H1 blocker.¹⁹

Comments and Limitations

The addition of ranitidine did not add any benefits to diphenhydramine treatment of acquired angioedema.

Is ecallantide more effective than placebo in the treatment of acute hereditary angioedema?

Ecballantide (Kalbitor/Dx-88; Dyax, Cambridge, MA) is a potent and specific recombinant protein inhibitor of plasma kallikrein. It is a clear and colorless, sterile, and non-pyrogenic solution. By directly inhibiting plasma kallikrein, it reduces the conversion of HMW kininogen to bradykinin. Ecballantide has no significant effect on the QTc interval, heart rate, or any other components of the ECG. A maximum plasma concentration of 586 ± 106 ng/mL was observed approximately 2–3 h after single 30 mg subcutaneous injection. Its mean elimination half-life is 2.0 ± 0.5 h. In December 2009, the US FDA approved ecballantide for the treatment of acute attacks of hereditary angioedema in patients aged 16 years and older after a clinical trial (Evaluation of DX-88_s Effect in Mitigating AngioedemaSM 4 or EDEMA4 study).³⁶ Side effects include dizziness, fatigue, headache, nausea, vomiting, increased liver function tests, and prolonged partial thromboplastin time.

Efficacy and Safety

In the EDEMA1 trial, Schneider and colleagues sought the best dose for ecallantide. They compared intravenous injections of ecallantide 5, 10, 20, and 40 mg/m² with placebo administration. Twenty-nine out of 40 patients responded to ecallantide (72.5%) whereas the response in the placebo group was 25%. The frequency of side effects was similar in the ecallantide and placebo groups.³⁷ In the EDEMA3 study, 72 patients were randomized to receive either 30 mg of subcutaneous ecallantide or placebo. The mean treatment outcome score was significantly better in the ecallantide group both after 4 h and 24 h. The same trend was noted for the mean symptom complex severity scores. Patients under ecallantide therapy experienced headache, diarrhea, pyrexia, and nasal congestion more often than the patients receiving the placebo. Drug-related adverse events occurred in both groups with no significant difference in frequency or severity.^{38, 39} EDEMA4 had a similar study design to EDEMA3. The sample size, however, was higher (96 patients), with the results being similar to those of the EDEMA3 study (Figure 11-1).^{36, 39}

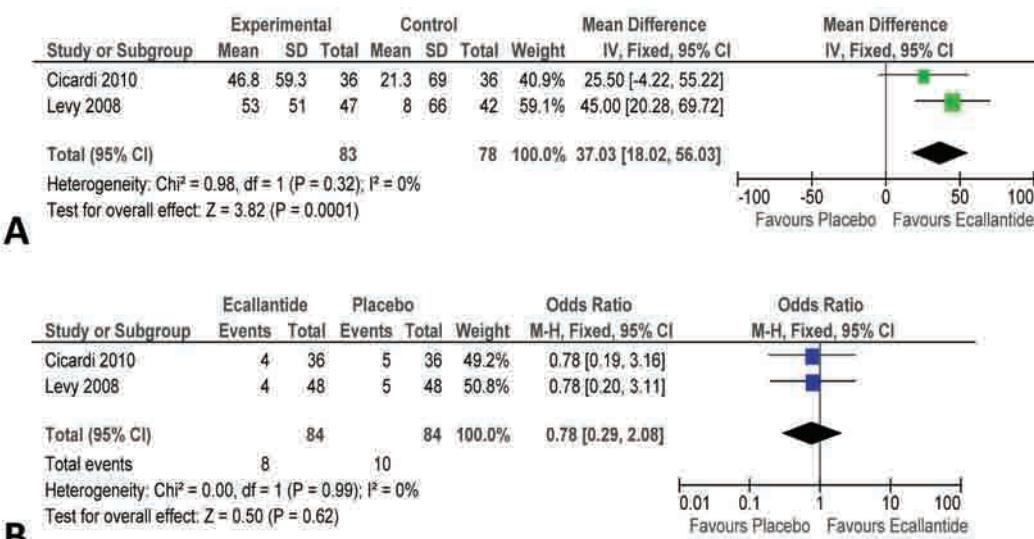


FIGURE 11-1 A. Forest plot, ecallantide vs. placebo, Outcome: treatment of outcome score at 4 hours.
B. Forest plot, ecallantide vs. placebo, Outcome: drug related Adverse Events.

Comments and limitations

Ecallantide may be considered as a first-line therapy for acute attacks of hereditary angioedema. It is well tolerated by the majority of patients; its most common side effects include nausea, fatigue, headache, and upper respiratory infections. Its only serious complication is anaphylaxis. This limits its self-administered application.

Is tranexamic acid more effective than placebo as a prophylaxis agent of nonhereditary angioedema?

Efficacy and Safety

In a preventive crossover study, patients were randomly assigned to receive either oral tranexamic acid (4.5 gm/day) or placebo for 3 months. After completion of the treatment

period, the total number of days with edema in the tranexamic acid and placebo patients were 36/854 (4.2%) and 88/403 (21.8%), respectively. After 4 years of follow up, the patients in the tranexamic acid group continued to show a good response. Side effects in the tranexamic acid group included frequent diarrhea and abdominal discomfort as compared to that in the placebo group.⁴⁰

Comments and Limitations

Oral tranexamic acid appears to be a good therapeutic agent for preventing acute attacks of non-hereditary angioedema.

Can heparin injection or inhalation prevent acute angioedema attacks in hereditary angioedema patients?

Since the 1970s, it has been suggested that heparin can change the dynamics of complement cascade.⁴¹

Efficacy and Safety

In one crossover RCT, the effects of subcutaneously injected calcium heparin (200 U/kg) were compared with those of inhaled calcium heparin and placebo. Subcutaneous injection of heparin did not prevent the attacks better than the placebo. Further, importantly, the patients who were received inhaled heparin responded worse than the placebo group. The main side effects included injection site reactions, headache, upper respiratory tract infections, knee pain or stiffness, sore throat, and bruising of various body parts. Injection site reactions were the only drug-related adverse effects. There were no serious drug-related adverse events due to the short duration of the heparin therapy.⁴²

What We Know: Acute Urticaria

- The exact pathophysiology of acute urticaria is unclear. Several different triggers can induce it. (see Table 11-1)
- There is no placebo-controlled trial to prove the efficacy of H1 or H2 antihistamines in the treatment of acute urticaria.
- H2 antihistamines are as effective as H1 antihistamines and the combination therapy of H1 and H2 can be beneficial.
- Short-term (less than 4 days) low dose oral corticosteroid therapy can be useful in severe acute urticaria cases.

What We Know: Angioedema

- For non-hereditary angioedema, the first step is to remove any potential trigger.
- Evidence for acute attacks of nonhereditary angioedema is extremely weak. The only relevant randomized trial showed no benefit for addition of ranitidine to diphenhydramine in the treatment of allergic angioedema.
- Evidence for prophylactic therapy of acquired angioedema is weak too. In the only trial, tranexamic acid was proven to be a good prophylactic agent for nonhereditary angioedema.
- Although it has not been supported by RCTs, it is highly recommended to develop training programs for angioedema patients to self administer the drugs to either prevent or quickly treat acute attacks.
- Although attenuated androgens are the first prophylaxis choice for hereditary angioedema, there is no strong evidence to support it.
- C1-INH can be prescribed to prevent attacks of hereditary angioedema (in nano-filtered form) and also to treat the acute form of it (all types including recombinant form).
- Two new drugs of Icatibant and Ecallantide are effective and safe for the treatment of acute attacks of hereditary angioedema.

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Comments and Limitations

Injected or inhaled heparin could not prevent acute attacks of hereditary angioedema.

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Treatment of Chronic Urticaria

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INTRODUCTION

Chronic urticaria (CU) is a common condition faced by both dermatologists and allergists alike. Numerous therapies have been used to treat CU with antihistamines being the best studied. However, many patients with CU are only partially responsive to antihistamines. The intent of this chapter is to review the evidence for both antihistamine and alternative, nonantihistamine therapies in the treatment of CU.

EPIDEMIOLOGY

The epidemiology of urticaria has not been adequately studied and data are especially lacking for the United States. In the United States, anecdotally there appears to be an increase in CU patients within many practices. Approximately 20% of the population may have acute urticaria at some point in their lives. This statistic has not changed much from a study conducted in 1969 in England¹ to a more recent telephone survey in Spain from 2004.² The prevalence of CU in the general population has not been adequately studied. In the aforementioned Spanish telephone survey, 0.6% of respondents gave a history consistent with CU. Anecdotally, many allergists in the U.S. feel there has been an increase in the number of patients they are seeing with CU, but whether this is indeed fact or perception remains to be proven. One German study found that ~3% of both a general practitioner's patients as well as a dermatologist's patients had some form of urticaria.³

ETIOLOGY

While numerous etiologies for CU exist, in the majority of cases, no cause can be found and hence a diagnosis of chronic idiopathic urticaria (CIU) is made. Approximately 30–40% of patients with CU have evidence of autoantibodies, including autoantibodies to the high-affinity IgE receptor (Fc ϵ RI) and rarely anti-IgE antibodies.⁴ These patients may be classified as having chronic autoimmune urticaria.^{5,6} Physical urticarias may often be distinguished by historical features of not only the triggering physical stimulus, but also the duration of the urticarial lesion itself. Individual physical urticaria lesions typically last between

30 minutes to 2 hours. In contrast, lesions of other types of CU, typically last most of the day. Other etiologies of CU are less common including urticarial vasculitis and rarely other systemic diseases.

SEARCH METHODOLOGY

A search of the medical literature was performed using the electronic databases of MEDLINE (OVID) and PubMed from 1966–2009, using search terms of urticaria, therapy, as well as individual names of different therapeutic agents or classes. Reference lists from the already identified studies were reviewed for additional, appropriate studies. Articles not published in English were excluded. Therapies available in the U.S. are the focus of this chapter.

THERAPIES

Avoidance Measures

Many patients with CU may have nonspecific triggers that aggravate their urticaria. Nonsteroidal anti-inflammatory drugs (NSAID) may exacerbate urticaria in 20–30% of CU patients.^{7–9} Avoidance of aspirin and other NSAIDs is recommended for patients with a history of NSAID-induced exacerbation of their CU and may be considered in other patients where this history is less clear. However, studies to evaluate the efficacy of NSAID avoidance on outcomes in CU are lacking. Heat is another common trigger for CU patients as is tight clothing, the latter more of a problem for patients with DPU. Opiates are known to cause non-IgE mediated reactions and have the potential to exacerbate urticaria in some CU patients. A small study of 25 CU patients showed very rare reactions to challenges with codeine.¹⁰ While avoidance of these factors is often recommended, no evidence exists as to the efficacy of avoiding these potential triggers.

DIETARY MANIPULATION

IgE-mediated food reactions are not a cause of CU and testing for food allergy is not necessary.¹¹ Although chronic urticaria is not a manifestation of IgE-mediated food allergy, some authorities have suggested that certain substances

in food may exacerbate or even be the cause of CU. This is believed to be caused by the presence of “pseudoallergens,” which are substances in food that exacerbate CU. Pseudoallergens include artificial preservatives and dyes in processed foods, as well as naturally-occurring aromatic compounds in certain foods (many fruits and vegetables, seafood, others). Aromatic compounds in wine, tomatoes, and spices as well as phenols such as p-hydroxybenzoic acid, citrus and orange oil, and salicylates have all been identified as pseudoallergens.¹² The evidence for pseudoallergen-free diets in CU has been evaluated in uncontrolled studies.^{13,14} One study concluded that adherence to a diet low in pseudoallergens was helpful, since 73% of 64 CU patients had either cessation or a significant reduction of symptoms within two weeks of adopting a pseudoallergen-free diet.¹³ However, only 19% of those who improved developed symptoms when subsequently challenged with individual pseudoallergens on provocation tests. In contrast to the high rates of response in this study, a subsequent larger study of 140 patients placed on a pseudoallergen-free diet found that only 28 percent had a strong or partial response.¹⁴ The largest study on this topic studied 838 patients with chronic urticaria and all underwent a food-additive-free diet. Thirty-one percent of subjects noted improvement in CU but none had complete remission. Double-blind placebo-controlled challenges were performed to both mixes of additives and individual additives in all subjects with a favorable response to diet, as well as a subset of those with no improvement on the diet. Overall, only 1–3% of patients had confirmatory double-blind challenges. Overall, the evidence is weak that pseudoallergen-free diets improve CU and given the difficulty of adhering to these diets, their use in all CU patients is not recommended.

TOPICAL THERAPIES

Potent topical corticosteroids have been shown to reduce mast cell numbers and response to stroking the skin in a study of six patients with dermographism.¹⁵ Other relatively small studies have shown clinical improvement in patients with localized delayed pressure urticaria treated with different preparations of potent topical corticosteroids.^{16,17} An open trial in CIU patients with topical corticosteroids showed only short-term improvement in symptoms.¹⁸ These studies suggest that topical corticosteroids may be beneficial in patients with localized delayed pressure urticaria but have limited utility and long-term efficacy for treating diffuse urticaria and are not recommended for chronic idiopathic urticaria.

SYSTEMIC THERAPIES

While numerous systemic therapies have been used to treat patients with chronic urticaria, the majority of systemic therapies have not been extensively studied with the exception of H1 antihistamines. There is a wide range of levels

of evidence as well as quantity and quality of evidence for these therapies. In addition, the safety of these therapies varies widely as does cost. Table 12-1 summarizes the evidence, potential adverse effects, and cost for several therapies in chronic urticaria.

H1 ANTIHISTAMINES

H1 antihistamines are widely considered the cornerstone of pharmacotherapy for CU.^{19,20} Most symptoms of urticaria are primarily mediated by H1-receptors located on nerves and endothelial cells and therefore H1-antagonists are logical mainstays of therapy for urticaria. Both first and second-generation antihistamines have been used in the treatment of urticaria. Patients with CU show variable responsiveness to antihistamines. In a study involving 390 patients with urticaria, the majority of which had CU, 44% of patients reported a good response to H1-antagonists.²¹ A cross-sectional survey of 98 CU patients treated with antihistamines (mostly first-generation) reported that 94% experienced short or long-term control of pruritus.²²

A number of large, double-blind, placebo-controlled, randomized studies have demonstrated the safety and efficacy of second-generation antihistamines in improving symptoms of chronic urticaria, as well as disruption of sleep and daily activities. Each of the currently available 2nd generation antihistamines in the United States has been shown to be effective in these types of studies in CU including loratadine,²³ cetirizine,^{24,25} fexofenadine,^{26,27} desloratadine,²⁸⁻³¹ and levocetirizine^{32,33} Amongst agents used to treat CU, 2nd generation antihistamines have the most robust evidence for safety and efficacy and are widely endorsed by international guidelines as first-line agents to treat CU.^{19,20,34}

Relatively few studies have compared the efficacy amongst the currently available 2nd generation agents. An open label study treated 50 CU patients consecutively with cetirizine and found 45 who achieved complete symptomatic control.³⁵ Thirty of these 45 complete cetirizine responders completed a 6-week open-label trial with levocetirizine. Similar control was achieved for wheal and flare but significantly less control of itch than with cetirizine. A large, randomized, double-blind, multi-center study compared levocetirizine 5 mg with desloratadine daily for 4 weeks in 886 patients with CIU.³⁶ While both agents showed clinically significant improvement in the Dermatology Life Quality Index, levocetirizine showed greater improvement in pruritus scores and CIU composite scores than desloratadine. A randomized double-blind study compared cetirizine 10 mg versus fexofenadine 180 mg daily for 6 weeks in 116 patients with CU.³⁷ A higher percentage of patients were symptom free with cetirizine (52%) than with fexofenadine (4%) with similar rates of adverse effects. Overall, the evidence favors cetirizine and levocetirizine; however, more well-designed clinical trials are required to confirm this.

Many patients with CU may not respond adequately to typically recommended doses of second-generation

TABLE 12-1—Evidence for Therapies in Chronic Urticaria

Drug	Level of Evidence	Quality & Amount of Evidence	Potential for Serious Adverse Effects	Cost
H1 antihistamines	Ia	High	Low	Low
H2 antihistamines	Ib	Low	Low	Low
doxepin	Ib	Moderate	Low	Low
Systemic corticosteroids	IV	Low	High	Low
Leukotriene modifiers	Ib	Moderate	Low	Moderate
dapsone	IIb	Low	Moderate	Low*
sulfasalazine	III	Low	Moderate	Low*
hydroxychloroquine	Ib	Low	Low	Low
colchicine	III	Low	Low	Low
Calcineurin inhibitors	Ib	Moderate	High	High*
mycophenolate	IIb	Low	Moderate	High*
omalizumab	Ib	Low	Moderate	High
IVIG	IIb	Low	Moderate	High*
Beta-agonists	Ib (no effect) III (effect)	Moderate Low	Moderate	Low
NSAIDs	III	Low	Moderate	Low
Methylxanthines	Ib	Moderate	Moderate	Low*
Phototherapy	Ib	Moderate	Moderate	High
Androgens	Ib	Low	Moderate	Moderate*
Methotrexate	III	Low	High	Low*
Anticoagulants	III	Low	High	Low*

Category of evidence (modified from Shekelle et al.(280)): Ia = evidence for meta-analysis of randomized controlled trials or systematic reviews of randomized controlled trials; Ib = evidence from at least one randomized controlled trial; IIa = evidence from at least one controlled study without randomization; IIb = evidence from at least one other type of quasi-experimental study; III: evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case-control studies; IV = evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

Quality and Amount of Evidence stratified based on both number of studies as well as quality of studies.

* = require laboratory monitoring which would increase cost

antihistamines. Limited data are available on dosing second-generation antihistamines at higher than the recommended amounts. Studies evaluating cetirizine in doses ranging from 20 to 30 mg/day showed conflicting results. An open study of 21 CU patients with inadequate response after 1-2 weeks of cetirizine 10 mg daily were treated with cetirizine 10 mg twice daily for 1-2 weeks.³⁸ The subjects were randomized to continue either cetirizine 20 mg daily or reduce to 10 mg daily for an additional 1-2 weeks. Both groups had improved urticarial scores on cetirizine 20 mg daily with continued improvement in the group that remained on the higher dosage but worsening symptoms in the group whose cetirizine dosage was reduced to 10 mg daily. In contrast, a similarly sized study evaluated 22 CIU patients with histories of failing two or more 2nd generation antihistamines who were treated with cetirizine 10 mg daily for 1 week, then the dosage was increased to 10 mg three times daily.³⁹ Only one of the 22 patients had benefit with increased doses of cetirizine, while the others were eventually treated with systemic steroids, cyclosporine,

or cyclophosphamide in one case. A multicenter trial of 418 patients treated with fexofenadine at doses of 20 mg, 60 mg, 120 mg, or 240 mg twice daily found that the three higher doses provided better disease control than the lowest dose, but there were no significant differences in effectiveness among the higher doses.²⁷ Recently a study of 30 patients with acquired cold urticaria evaluated patients in a randomized, placebo-controlled, cross-over study comparing desloratadine 5 mg daily with desloratadine 20 mg daily versus placebo using cold provocation testing and objective outcomes.⁴ While both doses of desloratadine showed efficacy, the 20 mg dosage showed greater efficacy than the 5 mg dosage. Finally, a recent study enrolled 80 patients who had histories of failing antihistamine therapies into a double-blind randomized trial of levocetirizine or desloratadine.⁴¹ Daily doses were increased weekly from 5 mg to 10 mg then 20 mg at weekly intervals. Subjects left the study when they became symptom free. At the end of 3 weeks if subjects failed 20 mg of either levocetirizine or desloratadine, they were crossed over to receive the other

medication. Interestingly 13 patients became symptom free on standard 5 mg doses of either medication raising issues of prior adherence with therapy. In comparison, 28 subjects became symptom free on the higher doses of 10 mg (8 levocetirizine vs. 7 desloratadine) and 20 mg (5 levocetirizine vs. 1 desloratadine). Of the 28 patients nonresponsive to 20 mg desloratadine, seven became symptom-free with 20 mg levocetirizine. None of the 18 levocetirizine nonresponders benefited with 20 mg desloratadine. Interestingly, there were no reports of increased somnolence with these higher doses in either treatment group. Recent international guidelines for CU have recommended using second-generation antihistamines in doses up to four-fold higher than recommended¹⁹, though the evidence for this approach is limited.

First-generation antihistamines have also been used to treat urticaria. Double-blind placebo-controlled studies have demonstrated efficacy for several first-generation antihistamines in CU with overall similar efficacy to second-generation antihistamines.^{24,42,43} First-generation antihistamines have been recommended as add-on therapy to CU patients who have had inadequate control on second-generation antihistamines, however studies to demonstrate efficacy of this approach are lacking.^{44,45} Sedation and impairment are well documented with first-generation antihistamines. While the degree of impairment varies amongst first-generation antihistamines, as a group they cause significantly greater impairment of cognition and psychomotor function than second-generation antihistamines.⁴⁶ Sedating antihistamines are often recommended to be dosed as a single nocturnal dose in an attempt to reduce daytime impairment.⁴⁷ Data are lacking regarding whether this approach does reduce daytime somnolence especially when given chronically to patients with CU. Studies evaluating subacute use of first generation antihistamines have shown tolerance to performance impairment after 3-5 days of therapy.⁴⁸⁻⁵⁰ In addition to sedation and cognitive impairment, anticholinergic side effects including dry mouth and urinary retention are more common with first-generation antihistamines.

H2 ANTIHISTAMINES

H2-receptor antagonists have also been used to treat urticaria in conjunction with H1-receptor antagonists. Most studies demonstrating efficacy of H2-antagonists added to H1-antagonists in CU have been performed with cimetidine.⁵¹⁻⁵³ Cimetidine is an inhibitor of a number of cytochrome p 450 isoenzymes including those that are involved with metabolism of first-generation antihistamines. Plasma concentrations of hydroxyzine are higher in combination with cimetidine than with hydroxyzine alone.^{54,55} The increased serum hydroxyzine levels seen with concomitant cimetidine therapy also show enhanced suppression of histamine induced wheal and flare responses.⁵⁵ These effects were not seen with cimetidine and cetirizine. This

pharmacologic interaction may explain the perceived additional benefit of H2-antagonists in CU. Studies evaluating the combination of H1-antagonists and ranitidine in CU have yielded conflicting results in regards to an additive effect.^{56,57} A recent single-blind comparative trial using famotidine (which does not affect p-450 metabolism) in combination with hydroxyzine showed improvement compared to hydroxyzine plus cetirizine but was limited by the small and disproportionate number of evaluable subjects at the end of the study (19 in famotidine group and 7 in cetirizine group).⁵⁸ Overall, the evidence is weak supporting additional efficacy of adding H2 antihistamines to H1 antihistamines in CU therapy.

DOXEPIN

Doxepin is a tricyclic antidepressant with both H1 and H2 receptor antagonist properties. It has particularly potent H1 antagonist activity with in vitro studies showing 800 times more potent antagonism for the H1 receptor than diphenhydramine.⁵⁹ A double-blind cross-over study of 50 CIU subjects randomized to doxepin 10 mg three times daily or diphenhydramine 25 mg three times daily demonstrated superiority of doxepin with partial or total control achieved in 74% of subjects on doxepin versus only 10% treated with diphenhydramine.⁶⁰ Doxepin was noted to be half as sedating as diphenhydramine. Another small study in idiopathic cold urticaria patients comparing doxepin 10 mg with cyproheptadine 4 mg and hydroxyzine 10 mg (all administered three times daily) showed similar efficacy in regards to suppression of the ice cube test but less adverse effects with doxepin.⁶¹ Since doxepin has a half-life of 13 hours⁶² it may be dosed once a day, and because of its potential for sedation is often recommended at bedtime.⁶³ Data are lacking in regards to the addition of doxepin with other 2nd generation antihistamines although this strategy is often used.⁶⁴

SYSTEMIC CORTICOSTEROIDS

Systemic corticosteroids are frequently used in patients with CU refractory to antihistamine therapy. Nonetheless, no controlled trials have demonstrated the efficacy of systemic corticosteroids in CU. One study evaluated the role of a steroid taper but not compared to placebo. This study of 40 patients with delayed pressure urticaria (DPU) compared a combination of nimesulide and ketotifen with a 7 week taper of prednisone and found similar results.⁶⁵ Thirty percent of subjects withdrew from the prednisone treatment group due to adverse effects. A prospective study of 17 patients with various types of CU who were taking systemic corticosteroids (3-30 days per month) evaluated the impact of corticosteroid withdrawal and ability to sustain control off corticosteroids.⁶⁶ They noted that 47% had a short relapse or worsening of their urticaria upon withdrawal of corticosteroids. The majority of patients

were able to remain off corticosteroids with either complete or partial remission with addition of H1-antagonists. Expert opinion varies on the role of systemic corticosteroids with some suggesting alternate day use for refractory patients,⁴⁴ and others including international consensus groups that systemic corticosteroids should be avoided for long-term treatment of CU, since dosages necessary to suppress symptoms are usually high with significant adverse effects.^{19,47} Given the predictable and significant side effects of systemic glucocorticoids, these drugs should be avoided for long-term use but may be needed as rescue therapy to gain control of severe symptoms.

ALTERNATIVE THERAPIES FOR CU

While antihistamines are the mainstay of therapy in CU, as many as 50% of CU patients may not achieve satisfactory control with antihistamine therapy.²¹ Systemic corticosteroids have predictable systemic toxicities that occur frequently in patients on chronic therapy. A number of therapeutic alternatives have been evaluated to treat anti-histamine refractory urticaria in order to reduce the need for systemic corticosteroids.^{67,68} The term alternative therapies are used to describe these various agents. While some of these therapies possess immunosuppressant, immunomodulatory, or corticosteroid-sparing activity, these properties do not apply to all of these therapeutic options and therefore these terms are not recommended to use to describe alternative therapies as a whole. Overall, the evidence for these alternative agents is limited, and large, well-designed studies are lacking. Special considerations for the use of these alternative agents include potential toxicity (both acute and long-term), cost, need for laboratory monitoring, and patient preferences.

Leukotriene Modifiers

Leukotrienes may have a role in the pathogenesis of some patients with urticaria. Leukotriene D₄ when injected into the skin is more potent than histamine in causing a wheal and flare.⁶⁹ Serum from patients with autoimmune CU has been shown to induce release of histamine and leukotriene production.⁷⁰ Leukotriene modifiers are one of the best studied groups of alternative agents for treatment of CU and are generally well-tolerated with rare significant adverse effects. Leukotriene receptor antagonists have shown efficacy in the treatment of CU in single and double-blind studies for zafirlukast and montelukast either as single agents or in combination with antihistamines.⁷¹⁻⁷⁷ Most of these studies had relatively small numbers of subjects ranging from 27-86 subjects with only one study involving 160 subjects.⁷⁷ However, a double-blind placebo controlled crossover trial with zafirlukast in 52 patients with CIU showed no benefit.⁷⁸ Most studies showing beneficial effects of leukotriene receptor antagonists have shown improvement within weeks of initiation. Studies

comparing the efficacy of leukotriene receptor antagonists with antihistamines have shown mixed results with some studies showing greater efficacy^{73,74} and others showing less efficacy⁷⁷ than second-generation antihistamines. In contrast to leukotriene receptor antagonists, 5-lipoxygenase inhibitors have not been studied in the treatment of CU with only rare anecdotes of success reported.^{79,80}

Several factors have been suggested to predict clinical response to leukotriene modifiers. The pathogenesis of aspirin/NSAID-exacerbated urticaria is linked to systemic overproduction of prostaglandin D₂ and cysteinyl leukotriene production.⁸¹ Initial case reports followed by randomized controlled trials have shown efficacy of montelukast in NSAID-exacerbated CIU patients with one study showing efficacy of montelukast greater than cetirizine.⁷⁴ An open study of 10 subjects with proven NSAID-induced urticaria underwent premedication with montelukast prior to ibuprofen challenge with three showing complete blockade and 6 with partial blockade of urticaria.⁸² Two randomized-controlled studies involving 27 and 95 CIU patients reported ASST positivity a predictor of better response to leukotriene modifiers.^{72,73} In contrast, an open trial suggested that shorter duration of CU and younger age were more predictive of response to leukotriene modifiers than either a history of NSAID exacerbation or positive ASST.⁸³ Montelukast has also been reported to be beneficial in three of five patients with urticaria that was induced or aggravated by antihistamines.⁸⁴

Leukotriene modifiers have been reported to have benefit in some physical urticarias. Case reports of leukotriene receptor antagonists either alone or in combination with antihistamines have suggested benefit in cold urticaria.^{85,86} Two randomized controlled trials have demonstrated superiority of a leukotriene receptor antagonist in combination with antihistamines over antihistamine monotherapy in patients with DPU.^{71,87}

Overall, while several controlled studies indicate efficacy of leukotriene receptor antagonists in CU, most studies are relatively small. Nonetheless, given the benign side effect profile of these agents and general tolerability, they may be considered in patients with unsatisfactory responses to antihistamine therapy.

Dapsone

Dapsone produces a variety of effects of potential relevance to both vasculitic and nonvasculitic urticaria. These effects include suppression of prostaglandin and leukotriene activity, interference with release or function of lysosomal enzymes⁸⁸ and myeloperoxidase generation of toxic halides,⁸⁹ disruption of integrin-mediated neutrophil adhesiveness,⁹⁰ inhibition of signals to recruit and activate neutrophils,⁹¹ and scavenging of oxygen free radical intermediates.⁹² Many of these activities may affect neutrophil function, however it is unclear whether dapsone has preferential response in neutrophil-rich urticaria.

Several case reports and case series have suggested benefit of dapsone in CIU, idiopathic angioedema, DPU, and urticarial vasculitis.⁹³⁻¹⁰⁰ A series of 11 patients with antihistamine unresponsive CU (3 with DPU) were treated with dapsone 25 mg daily in addition to cetirizine and instructed to withdraw cetirizine when satisfactory control of symptoms was achieved.⁹⁵ Nine patients (including the three DPU patients) had a complete response to the 25 mg dosage with another patient requiring 50 mg of dapsone for complete control. The majority of patients had a sustained remission of urticaria. Recently a randomized, unblinded study of 65 CIU patients compared dapsone and desloratadine versus desloratadine alone during 3 months of treatment with an additional 3 month post-treatment observational period.¹⁰¹ While the dapsone treated group had similar reductions in urticaria scores compared to the desloratadine monotherapy group, nine patients treated with dapsone had complete responses, whereas none of the control subjects did. Additionally, five of nine responders remained urticaria free 3 months after discontinuing dapsone suggesting that dapsone may induce remission of CU as has been suggested in some other reports.^{93,95}

Dapsone is usually well-tolerated but has predictable side effects including dose-related anemia. Less common adverse effects include peripheral neuropathy, rash, gastrointestinal complaints, hepatotoxicity, and rarely methemoglobinemia, blood dyscrasias or the syndrome of drug rash with eosinophilia and systemic symptoms.¹⁰² Prior to initiation of dapsone therapy, it is recommended to determine the level of glucose-6-phosphate dehydrogenase (G6PD) as dapsone should be avoided in G6PD-deficient patients due to risk of severe hemolysis. Ongoing laboratory monitoring for anemia and hepatotoxicity is recommended.¹⁰³

Overall, the evidence for the efficacy of dapsone in CU is limited. Case series and reports suggest efficacy and possibly remission. While generally well-tolerated, laboratory monitoring is required. My own experience with dapsone in CU has been favorable and I believe it is a reasonable alternative agent in antihistamine refractory patients.

Sulfasalazine

Sulfasalazine produces a variety of anti-inflammatory effects with potential relevance to urticaria pathogenesis including decreased prostaglandin D2 synthesis and histamine release from activated mast cells,¹⁰⁴ attenuation of the respiratory burst of polymorphonuclear leukocytes,¹⁰⁵ and inhibition of proliferation of B-lymphocytes.¹⁰⁶ Case reports and case series have suggested efficacy of sulfasalazine in patients with CU and DPU.¹⁰⁷⁻¹⁰⁹ A retrospective observational study of 19 CIU patients demonstrated significant improvement in 14 of 19 patients with more modest benefit in 4 additional patients.¹¹⁰ Therapeutic response occurred within 1 month and doses above 2 g/d had no additional benefit.

Gastrointestinal complaints including nausea, vomiting, dyspepsia and anorexia and headache are the most frequent complications of sulfasalazine therapy.¹¹¹ These symptoms typically occur early in therapy and are much more common in patients taking > 4 g/d (a dose usually not required for treatment of CU). Gradual escalation of dosing over several days may reduce the gastrointestinal effects. Hematologic abnormalities, proteinuria, and hepatotoxicity, are uncommon but laboratory monitoring for these adverse effects is recommended.¹¹² The potential for sulfasalazine to induce remission of urticaria is unknown.

Overall, the evidence for sulfasalazine in CU is very limited. It is typically a well-tolerated drug (other than gastrointestinal effects which are easily recognizable) and is inexpensive and therefore may be considered in patients with antihistamine refractory CU. My own personal experience with sulfasalazine in CU is that it may be occasionally effective and that serious adverse effects are rare with appropriate monitoring.

Hydroxychloroquine

Hydroxychloroquine is an anti-inflammatory agent that disrupts T-cell receptor crosslinking-dependent calcium signaling¹¹³ and disrupts antigen processing¹¹⁴ and therefore has potential benefit in CU. Limited data are available on the use of hydroxychloroquine in CU. A case report suggested efficacy in a patient with hypocomplementemic urticarial vasculitis.¹¹⁵ A randomized, blinded, placebo-controlled study of 21 subjects with CU demonstrated significant improvement in quality of life, but only trends towards improvement in urticaria activity scores or reduction in other medications.¹¹⁶ The study was underpowered to detect significant differences due to drop-outs.

Hydroxychloroquine is generally well-tolerated with the most worrisome adverse effect being retinopathy. The risk of retinopathy from hydroxychloroquine is exceedingly rare with less than 20 reported cases in over 1 million treated individuals.¹¹⁷ Almost all cases have occurred in individuals who have used the drug > 5 years. Many cases of toxicity involved dosages greater than 6.5 mg/kg/day. While recommendations vary, the most recent American Academy of Ophthalmology recommendations divide the type of evaluation based on low or high risk patients.¹¹⁷ High risk patients are identified as taking > 6.5 mg/kg/day, duration of use > 5 years, age > 60 years and presence of renal or liver disease or obesity. For low risk patients, a baseline examination during the first year is recommended with follow-up evaluations varying from every 2-4 years based on age.

Overall, evidence for hydroxychloroquine in CU is also very limited. It is typically well-tolerated and inexpensive but has a slow onset of action. My personal experience with hydroxychloroquine is that it is occasionally effective without serious adverse effects.

Colchicine

Amongst alternative agents, colchicine has been used relatively frequently to treat CU despite minimal evidence to support its use. Colchicine has some anti-inflammatory activities particularly as relates to neutrophils including suppression of neutrophil leukotriene B4 generation¹¹⁸ and expression of adhesion molecules on endothelium and neutrophils¹¹⁹ that could potentially play a role in CU. A single double-blind placebo controlled trial in 13 patients with DPU failed to show benefit of colchicine.¹²⁰ A recent open study treated CU patients according to histologic features of their CU and 8 of 9 colchicine treated patients with neutrophilic inflammation responded to colchicine.¹⁰⁰ Other case reports suggest efficacy in urticarial vasculitis patients.¹²¹⁻¹²³ Colchicine is generally well-tolerated with the most frequent adverse effect being diarrhea. High doses can cause bone marrow suppression and long-term use has rarely been associated with myopathy.¹²⁴

Overall, colchicine has very limited evidence supporting its use in CU. Other than diarrhea, it is typically well-tolerated and inexpensive. My personal experience with colchicine has been disappointing with rare beneficial effects in CU patients.

Calcineurin Inhibitors

Cyclosporine is another relatively well-studied alternative agent in CU. A wide spectrum of possible anti-urticularial

mechanisms has been described, including inhibition of calcium-dependent release of and responsiveness to histamine, leukotriene C4, and other mediators in various cell types, including mast cells.¹²⁵ Many of these hypothesized effects target the mast cell, but anti-T-lymphocyte activity with resultant disruption of autoantibodies and interaction with mast cells may be another mechanism of action in urticaria.¹²⁶ Cyclosporine may also disrupt TNF- α activity and secondarily inhibit neutrophil accumulation¹²⁷ as well as reducing levels of IL-2R and IL-5.¹²⁸ Tacrolimus has similar immunosuppressive activities as cyclosporine but binds to a different immunophilin, FK506 binding protein, and this complex inhibits calcineurin phosphatase.¹²⁹ Like cyclosporine, tacrolimus has been shown to inhibit mediator release from mast cells.¹³⁰

The first published experience described dramatic improvement in three patients (2 also with an angioedema component) but who discontinued therapy because of intolerance of the relatively high dose used (6 mg/kg daily), with relapse of their CIU.¹³¹ Subsequently, several other case reports and case series have used lower doses sometimes with downward titration of dosing to maintain efficacy and reduce adverse effects^{128,132,133} A recent case series suggests efficacy in pediatric patients with CU¹³⁴ Evidence on cyclosporine in physical urticarias is limited to single case reports for cold¹³⁵ and solar¹³⁶ urticaria.

Three randomized controlled studies have demonstrated the efficacy of cyclosporine in CU patients.¹³⁷⁻¹³⁹ Comparisons of these studies are shown in Table 12-2.

TABLE 12-2—Randomized, Controlled Studies on Cyclosporine in CU

	Grattan et al.(137)	DiGioachhino et al.(138)	Vena et al.(139)
Total subjects	30	40	99
# randomized to CSA	20	20	64
Dose of CSA	4 mg/kg/day	5 mg/kg/day for 8 weeks then 4 mg/kg/day for 8 weeks	5 mg/kg/day for 2 weeks then 4 mg/kg/day for 2 weeks then 3 mg/kg/day for 12 weeks
Duration of controlled study therapy	4 weeks	2 weeks	16 weeks
ASST only subjects	yes	yes	not stated
Primary outcome	Reduction of urticaria activity score to <25% of baseline at 4 weeks	Not stated	Change in urticaria severity score at 8 weeks
Primary Results	Responders CSA: 8/19 PBO: 0/10	"Responders" after 2 weeks: CSA: 20/20 Cetirizine: 4/20	Improved severity scores after 8 weeks: CSA: 62% PBO: 23%
Adverse effects	29/30 none stopped therapy	3 reversible rise in creatinine 4 other adverse effects	CSA: 44/64 PBO: 16/35 6 had rise in creatinine
Comments	7/10 nonresponders to placebo, responded to CSA in open label extension	Study severely limited due to crossing-over of control group after 2 weeks and most of data comparing data pre and post CSA	Statistical improvements in Dermatology Life Quality Index in CSA vs. PBO

CSA: cyclosporine; ASST: autologous serum skin test; PBO: placebo

Two studies randomized patients to either cyclosporine or placebo,^{137,139} while one study¹³⁸ used cetirizine as a comparator. Doses used varied from 3–5 mg/kg/day. The main limitation of these studies was the definition of refractory CU as poor response to antihistamines or modest doses of cetirizine. Often in clinical practice, measures that are more aggressive are used to treat CU patients prior to resorting to cyclosporine and it is unclear based on these controlled studies whether cyclosporine would be as effective. One study was limited by the comparator group being switched over to open label cyclosporine therapy after only 2 weeks.¹³⁸

The optimal duration of therapy with cyclosporine is unclear with some recommending longer therapy to sustain benefit,^{139,140} with follow-up in the literature extending out as far as a mean of 11 years, while others suggest most of the benefit is apparent by the initial month of treatment.¹⁴¹ Studies evaluating using a positive ASST as a predictor of response to cyclosporine have found no correlation.¹⁴¹ Advantageous properties of cyclosporine include rapid onset (sometimes within days),^{133,138,142} possibility of long-lasting remission,^{135,138} and degree of efficacy comparable to prednisone.¹⁴²

Tacrolimus is another calcineurin inhibitor that has been evaluated in CU. A pilot observational study of tacrolimus in 12 patients with CIU poorly responsive to antihistamines reported 70% of patients responded to tacrolimus with 3 patients having resolution of urticaria, including one who had not responded to cyclosporine.¹⁴³

A number of adverse effects have been associated with calcineurin inhibitors including hypertension, renal dysfunction, headache, hypertrichosis, gingival hyperplasia, paresthesias, gastrointestinal symptoms, and metabolic abnormalities.¹⁴⁴ Many of these adverse effects are dose and/or duration related. Malignancies have been rarely reported with calcineurin inhibitors. A prospective long-term cohort study of 1252 patients with psoriasis treated with cyclosporine were followed up to 5 years and found a higher incidence of skin malignancies but not other nonskin malignancies.¹⁴⁵ Monitoring of blood pressure, renal function, serum drug levels, and other metabolic factors are important in patients treated with calcineurin inhibitors.¹⁴⁴

Overall, calcineurin inhibitors have the most abundant literature of available alternative agents with several controlled studies showing efficacy. My own experience with these agents is consistent with the previously discussed findings that these agents are frequently effective (including patients refractory to other alternative agents), have a rapid onset of action, are capable of inducing long-lasting remission, and are generally well tolerated. Nevertheless, due to their frequency of adverse effects and potential for serious adverse effects, I personally do not typically recommend calcineurin inhibitors as first-line alternative agents.

Mycophenolate

Mycophenolate mofetil (MMF) is an immunosuppressant used in transplantation as well as a growing number of autoimmune diseases. The active metabolite of MMF is a competitive inhibitor of inosine-5'-monophosphate dehydrogenase, and kills activated lymphocytes through the activation of a caspase-independent necrotic signal.¹⁴⁶ In an open-label study of 9 patients with CU with positive ASST refractory to H1 and H2 antagonists, 12 weeks of MMF 1000 mg twice daily showed significant improvement in urticarial scores, reduction in antihistamines and steroid sparing activity.¹⁴⁷ The most common adverse effects with MMF include gastrointestinal disturbances occurring in up to 20% of patients at doses of 2 g daily.¹⁴⁸ Hematologic side effects including leukopenia are less common, usually mild, reversible and dose related.

Overall, the evidence for mycophenolate in CU remains minimal. While often used as an alternative to other immunosuppressants (due to its better tolerability) for other diseases, its role in the treatment of CU is unclear but likely can be considered when other immunosuppressants are being contemplated. My personal experience with this agent has been that it has been effective in some patients with minimal adverse effects.

Omalizumab

Omalizumab is a recombinant humanized monoclonal antibody that binds to free IgE and inhibits binding of IgE to Fc ϵ RI, the high-affinity IgE receptor. Omalizumab reduces the number of Fc ϵ RI receptors on the surface of mast cells and basophils.¹⁴⁹ Several case reports have suggested efficacy of omalizumab in a variety of types of CU including cold urticaria,¹⁵⁰ cholinergic urticaria,¹⁵¹ solar urticaria,¹⁵² urticarial vasculitis,¹⁵³ idiopathic,¹⁵⁴ and idiopathic angioedema.¹⁵⁵ Recently, a proof of concept study evaluated the efficacy of omalizumab in 12 patients with CAU.¹⁵⁶ This was a single-blind study that included a 4-week placebo phase followed by omalizumab every 2 or 4 weeks for 16 weeks. Seven patients had complete resolution, four had partial improvement and 1 had no response. Preliminary evidence from double-blind, placebo-controlled studies of omalizumab also indicate efficacy in CU patients.¹⁵⁷ The mechanism of action of omalizumab is not clear and reports of efficacy have included patients without detectable autoantibodies and low total IgE levels.¹⁵⁸ Omalizumab is generally well-tolerated with rare reports of anaphylactic reactions occurring.

While the current evidence for omalizumab in CU is limited, there appears to be a growing body of evidence suggesting efficacy. This may certainly lead to new discoveries on pathogenesis of CU. Omalizumab is typically well-tolerated but expensive and may not be covered for urticaria treatment by many third party payers. Its potential for

remission of CU is also unclear. My personal experience with omalizumab indicates a high degree of efficacy but with return of urticaria upon discontinuation.

Intravenous Immunoglobulin (IVIG)

Intravenous immunoglobulin has a variety of immunomodulatory activities that theoretically may be important in CU including modulation of adhesion, complement function, cytokine levels, autoantibodies and anti-idiotype networks.¹⁵⁹ The earliest report of use of IVIG in CU involved an open-label trial of 10 patients with positive ASST and basophil histamine release tests who had failed other therapies including alternative agents.¹⁶⁰ Patients were treated with an immunomodulatory dose of IVIG, 0.4 g/kg/day for 5 consecutive days. Benefit was noted in 9 of 10 patients with three patients experiencing prolonged remission with 3 years of follow-up. Other case reports have suggested benefit of IVIG with various dosing regimens,^{161–163} however there are other reports of IVIG failures, particularly in urticarial vasculitis.^{164,165} A low-dose regimen of .15 g/kg every 4 weeks was reported to be effective in an open label study of 29 patients with autoimmune CU.¹⁶⁶ IVIG has also been reported to be beneficial in DPUA,¹⁶⁷ solar urticaria,¹⁶⁸ and urticarial vasculitis.¹⁶⁹ IVIG is relatively safe with predictable infusion-related adverse reactions including headache, myalgias, and nausea and rarely anaphylactoid reactions, aseptic meningitis or renal failure.

Overall, data are limited on the efficacy of IVIG. While typically well-tolerated, it is expensive and requires prolonged infusions. My personal experience with IVIG in CU has been disappointing.

Other Biologic Therapies

In addition to omalizumab, other biologic therapies have been reported to be helpful in case reports of refractory CU patients. A patient with DPUA was noted to have a rapid response when treated with the tumor necrosis factor inhibitor, etanercept for psoriasis.¹⁷⁰ His response persisted when switched to infliximab due to inadequate control of psoriasis. Numerous case reports have shown efficacy of the interleukin-1 receptor antagonist, anakinra, for the autoinflammatory syndrome, Schnitzler syndrome characterized by urticaria, fever, bone pain and monoclonal IgM gammopathy.^{171–173} Anakinra has also been reported to be beneficial in urticarial vasculitis.¹⁷⁴ Rituximab is a monoclonal antibody targeted against CD20 transmembrane protein on the surface of mature B cells. Individual case reports of efficacy of rituximab have recently been reported in patients with CAU¹⁷⁵ and urticarial vasculitis.^{176,177} In contrast, a case report of a failure of rituximab was reported in a severe steroid dependent CU patient who was resistant to numerous other alternative agents.¹⁷⁸

While these case reports are interesting, data are severely limited on these biologic therapies and with the exception of the treatment of Schnitzler syndrome, they should mainly be considered for patients proven refractory to other alternative agents.

Beta-Agonists

Beta-agonists have well-known inhibitory effects *in vitro* on mast cells including inhibition of mediator release.¹⁷⁹ However, studies of their *in vivo* effects on the skin have shown variable, limited and dose-related inhibitory effects on wheal and flare responses when injected into the skin prior to challenge with allergen, histamine or compound 48/80.¹⁸⁰ A small double-blind cross-over study of the cutaneous effects of oral terbutaline showed attenuation of the wheal response to injected allergen, but no effect on response to injection of histamine in 8 horse-allergic individuals. This same study also found that 2.5 mg terbutaline three times a day for 1 week had no effect on cold provocation in five subjects with cold urticaria. A more recent double-blind, double-dummy study similarly found that orally administered terbutaline or its pro-drug bambuterol did not inhibit mast cell activation or allergic skin responses.¹⁸¹

Reports on the efficacy of beta-agonists in CU have been mixed. An observational study of 24 patients with various forms of CU resistant to antihistamine therapy found terbutaline dosed 25 mg three times daily was more effective than antihistamines.¹⁸² Other case reports suggested efficacy with terbutaline and ketotifen in combination, in cold and other forms of CU.^{183,184} However, two double-blind studies have not shown significant benefit of terbutaline in CU.^{52,185} One study evaluated 18 patients with CU and found terbutaline no different than placebo.¹⁸⁵ Another double-blind, multiarm, crossover study of 19 CU patients found terbutaline inferior to antihistamine therapy.⁵² The most common adverse effects associated with oral beta agonist therapy are agitation, insomnia, tremulousness and tachycardia.

Overall, small, placebo-controlled studies have not shown efficacy of beta-agonists in CU. Therefore, it is unlikely that oral beta-agonists have a significant impact on most patients with CU, nevertheless they may be considered in select patients with refractory CU. My personal experience with beta agonists has been disappointing.

Non-steroidal anti-inflammatory drugs (NSAIDs)

Indomethacin is the main NSAID studied in CU and has been reported to be effective in an observational report of 10 patients with urticarial vasculitis.¹⁸⁶ In contrast, a double-blind, controlled, crossover trial of indomethacin therapy in 14 patients with delayed pressure urticaria revealed no

significant subjective improvement or reduction in area of induced wheals.¹⁸⁷ A study of topical indomethacin in 9 subjects with chronic dermatographia urticaria showed augmentation of dermatographia wheals.¹⁸⁸ The cyclooxygenase-2 inhibitor rofecoxib (withdrawn from the US market) showed efficacy in two small case series of CU patients,^{189,190} but no studies have been reported on the efficacy with the currently available cyclooxygenase-2 inhibitors in CU.

Overall, evidence for efficacy of NSAIDs in CU therapy is minimal. Since NSAIDs are a frequent cause of urticaria exacerbations, caution should be exercised when considering their use as alternative agents.

Methylxanthines

Few studies have evaluated the role of methylxanthines in CU. The earliest report of theophylline in 15 CU patients noted complete response in three, whereas six had no significant benefit.¹⁹¹ More recently, a larger double-blind, placebo-controlled study of 134 CU patients evaluated theophylline 200 mg twice a day for 6 months then 200 mg once a day for 6 months versus placebo as an add-on therapy to cetirizine.¹⁹² Both groups experienced large improvements in all symptoms assessed, however the treatment group had statistically significant improvement in overall urticaria scores but not pruritus. The clinical relevance of this statistical difference is unclear. These investigators also studied a group of 23 patients with DPUA using an open-label cross-over design and noted additional benefit over cetirizine during theophylline therapy.¹⁹³ An observational study of aminophylline plus terbutaline in 42 patients with cold urticaria showed overall improvement in the majority of subjects however 3 patients had to stop therapy due to cardiac events and 19 others had less severe adverse effects.¹⁹⁴

Overall, the evidence for the efficacy of theophylline in CU is modest at best. Nevertheless, it is usually well tolerated within its narrow therapeutic range and it is inexpensive. It certainly can be considered for antihistamine refractory CU patients, particularly as an add-on to antihistamines.

Phototherapy

Phototherapy includes ultraviolet-A (UVA) therapy with coadministration of psoralen (PUVA) or ultraviolet-B (UVB) therapy. Phototherapy may decrease histamine release from mast cells.¹⁹⁵ Phototherapy has been reported to be successful in various case reports of solar urticaria.¹⁹⁶⁻¹⁹⁹ Case series have reported benefit of phototherapy in other physical urticarias (cold, cholinergic, dermatographism) and CIU.²⁰⁰⁻²⁰² A relatively large retrospective study of 94 patients (88 with CIU) treated with narrow-band UVB (NB-UVB) demonstrated that 72% of treatment courses produced moderate improvement to

clearance of urticaria.²⁰³ Telephone follow-up years later revealed 33% of patients were clear of urticaria with 45% indicating improvement from NB-UVB therapy. Recently, an open-trial of 81 CU patients receiving levocetirizine with 48 randomized to additional NB-UVB therapy showed improvement in both groups but statistically larger treatment effects in the NB-UVB treated group.²⁰⁴ In addition, the NB-UVB treated group showed much lower scores 3 months later than those treated with levocetirizine alone. Adverse effects of phototherapy include erythema, pruritus, photodegenerative changes and increased risk for skin cancer.²⁰⁵

Overall, the evidence for phototherapy in CU is based on uncontrolled but relatively large case series and suggests efficacy in physical urticarias, especially solar urticaria in addition to CIU. Frequency of treatments and regional availability is a main obstacle of phototherapy but it certainly should be considered as an alternative agent.

Androgens

Androgens have an established role in the therapy for C1-esterase inhibitor deficiency syndromes. Danazol has immunosuppressive effects *in vitro* at physiologic concentrations showing inhibition of mitogen-induced lymphocyte proliferation.²⁰⁶ Several case reports suggest efficacy of androgens in physical urticaria including cholinergic urticaria^{207,208} and aquagenic urticaria.²⁰⁹ A randomized controlled trial found danazol effective in reducing exercise-induced wheals in 17 male patients with cholinergic urticaria.²¹⁰ Stanozolol was reported to be effective in a case series of five female patients with steroid-dependent CIU and was thought to induce remission in three of the patients. A relatively large, 12-week, randomized, double-blind, placebo-controlled study compared stanozolol 2 mg three times a day versus placebo in 58 CIU patients.²¹¹ The stanozolol group had a higher frequency of marked improvement (65% vs. 29%) and mean reduction in clinical scores. This study is limited by little information on prior therapy and the observation that both groups seemed to have a continued reduction in urticarial activity without a plateau by the end of the study. Androgens have a number of potential adverse effects including virilization, dysmenorrhea, weight gain, hypertension, hyperlipidemia, thrombotic complications, and rarely hepatotoxicity.

Overall, androgens have limited evidence to support their use. Since tolerability is generally better in males, these agents could be considered for refractory CU patients. My personal experience with androgens in CU has been disappointing.

Methotrexate

Methotrexate is an anti-inflammatory agent with unclear mechanisms of action that include increasing adenosine

levels, inducing apoptosis in activated CD4+ T-cells, and decreased neutrophil chemotaxis.²¹² Experience with methotrexate is limited with a few case reports and a case series the largest of which included 7 patients with CAU who noted benefit within 1-2 weeks of therapy.²¹³⁻²¹⁶ Methotrexate has potentially serious adverse effects including hepatotoxicity and pulmonary fibrosis and requires extensive laboratory monitoring. Given all of the above, its use should be restricted to CU patients who have failed numerous other safer alternative agents.

Anticoagulants

Recent studies have suggested that activation of the coagulation cascade via the tissue factor pathway leading to serum elevations in prothrombin fragments and D-dimer may have a role in the pathophysiology of CU.²¹⁷⁻²¹⁹ Therefore, anticoagulant therapy may have a therapeutic rationale in the treatment of CU. Warfarin has been reported in case reports to be efficacious in CU patients.²²⁰⁻²²² One study evaluated eight patients with CU treated in an open fashion with warfarin with a target International normalized ratio (INR) between 2.0-2.5.²²³ Six of eight patients showed improvement and three patients who had “dramatic” clinical improvement were treated in a double-blind manner and these subjects also showed efficacy during the periods on warfarin compared to placebo. A single case report found that three of four patients with concomitant angioedema had either no change or had worsening of their condition.²²⁴ One case report demonstrated that prophylactic subcutaneous heparin sodium dosed 5,000 IU twice daily was efficacious in a patient who failed warfarin.²²⁵ Treatment with warfarin carries the risk of hemorrhage, which can potentially be life-threatening and requires frequent monitoring of the INR.

Overall, the evidence for anticoagulants in CU therapy is minimal and primarily of theoretical benefit. Due to its risk for serious adverse effects, anticoagulant therapy should be reserved for CU patients who have failed numerous safer alternative agents.

Miscellaneous Alternative Agents

A number of other alternative therapies have been described in the treatment of CU including sirolimus,²²⁶ cyclophosphamide,²²⁷⁻²³⁰ gold,²³¹ plasmapheresis,²³²⁻²³⁷ cromolyn,^{238,239} and nifedipine²⁴⁰⁻²⁴³ and have been reviewed elsewhere.⁶⁸ Some agents have also been studied in CU with limited to no efficacy such as interferon alpha.^{244,245}

Choosing Alternative Agents for Treatment of Refractory Urticaria

There are several factors involved in selecting an alternative agent for refractory CU. First, it should be established

that the patient is indeed refractory to antihistamine therapy. Unfortunately, predictive factors for response to the vast majority of alternative agents are lacking. The presence of underlying comorbid factors may also play a role in determining an alternative agent. For example, in a patient with poorly controlled hypertension, a calcineurin inhibitor may have higher risk of exacerbating the hypertension. A patient's tolerability to other medications may also influence drug selection. Baseline laboratories may be required to determine if any agents are contraindicated, such as dapsone and hydroxychloroquine in a patient with G6PD deficiency. Frequency of treatment-related visits (e.g. frequent phototherapy sessions) should also be considered as this may be an impediment for certain patients. The cost of alternative agents varies considerably and their affordability is another important treatment consideration. Rapidity of response to an alternative agent is another factor that influences choice. In patients suffering significant adverse effects from glucocorticoid toxicity, agents with slow onset of action (e.g. hydroxychloroquine) may not be optimal. Finally, the potential risk of a given alternative agent is extremely important and needs to be weighed against the patient's current quality of life and any adverse effects from current therapy for their CU. While on alternative therapies, appropriate laboratory monitoring if indicated, is important. Recent guidelines for laboratory monitoring of many of the rheumatic agents used in the treatment of CU have been proposed and are available online as a supplement.¹¹²

Step-based Therapies for CU

Step-based therapies for many chronic diseases have been recommended by various expert panels and are often widely used. In regards to treatment of CU, a step-based approach has only recently been developed in guidelines.¹⁹ Unfortunately, no step-based approach in CU has been evaluated in any controlled study and evidence for these approaches are based largely on expert opinion. My own personal approach to patients with CU is shown in Table 12-3.

Therapies for Specific Conditions Associated with CU

Helicobacter pylori Infection

Helicobacter pylori has been reported in recent years to be associated with CU. Recently a study of 35 CU patients (57% were positive for *H. pylori*) found an association with heavy bacterial colonization and intense gastric inflammation and severity of CU.²⁴⁶ Several studies have evaluated whether treatment for eradication of *H. pylori* improves urticaria in CU patients. Overall the results are conflicting with several studies favoring that *H. pylori* eradication is beneficial²⁴⁶⁻²⁵² and many others indicating it is not

TABLE 12-3—Example of Step-Based Therapy in Chronic Urticaria

Step 1	2 nd gen antihistamine (e.g., cetirizine)
Step 2	Higher dose 2 nd gen antihistamine (e.g., cetirizine 20-40 mg daily)
Step 3	2 nd gen antihistamine + 1 st gen antihistamine (hydroxyzine or doxepin dosed at bedtime up to 150 mg qhs)
Step 4	Antihistamines + leukotriene receptor antagonist
Step 5	Anti-inflammatory alternative therapy (e.g., dapsone, sulfasalazine, hydroxychloroquine)
Step 6	Immunosuppressant alternative therapy (e.g., tacrolimus, cyclosporine, mycophenolate)
Step 7	Biologic therapy (e.g., omalizumab)
Step 8	Other alternative therapies (e.g., phototherapy, IVIG, etc)

helpful.²⁵³⁻²⁶⁰ Currently it is unclear whether treatment of eradication of *H. pylori* improves urticaria.

Thyroid autoimmunity

For several decades, an association with thyroid autoimmunity and CU has been described.²⁶¹⁻²⁶³ Several reports have described clinical benefits of CU with treatment of these patients with thyroid hormone at doses that suppress the TSH level.²⁶⁴⁻²⁶⁶ A recent survey of U.S. allergists showed that while the majority tested for thyroid autoantibodies, the minority treated euthyroid patients.²⁶⁷ Controlled studies proving the efficacy of treating euthyroid patients with thyroid hormone are currently lacking.

Herpes Infection

Rare cases of urticaria associated with genital herpes have been reported with successful treatment with acyclovir²⁶⁸ and valacyclovir.²⁶⁹ Another case series of 12 patients with CIU, idiopathic angioedema, and HAE found that 5 patients responded to acyclovir therapy with recurrence with discontinuation of acyclovir.²⁷⁰ None had genital herpes but they did have elevated antibody titers to herpes simplex or Ebstein-Barr virus. Controlled studies proving the efficacy of anti-herpetic therapy on CU are currently lacking.

Hormone Sensitivity

Autoimmune progesterone dermatitis is a rare cyclical disease associated with the luteal phase of the menstrual

cycle with a variety of dermatologic manifestations including urticaria and angioedema.²⁷¹ The diagnosis can be confirmed through intradermal skin testing or intramuscular or oral challenge with progesterone.²⁷²⁻²⁷⁴ Case reports of successful treatment with conjugated estrogen,²⁷² gonadotropin-releasing hormone agonists,²⁷⁵ tamoxifen,²⁷³ and bilateral oophorectomy²⁷⁴ suggest that hormonal manipulation may be efficacious in some cases. Another even more rare form of hormone sensitivity is estrogen dermatitis, which is associated with premenstrual flares of dermatosis including urticaria in some cases.^{276,277} Patients with urticaria due to estrogen are diagnosed with intradermal skin tests to estrogen. Treatment with tamoxifen,^{276,277} bilateral oophorectomy,²⁷⁸ and progestin²⁷⁹ has been reported successful in some cases.

CONCLUSION

Antihistamines are first-line therapy and effective in the majority of cases of CU. Nevertheless, some patients with CU are antihistamine resistant and may require alternative agents for adequate control of their CU. The ultimate goal should be to control urticaria to reduce its impact on the quality of life of the patient, minimize adverse effects of medications, and eliminate chronic or frequent oral corticosteroids. While the evidence is limited for non-antihistamine therapies in CU, a rationale patient-based approach can be developed based on levels and quality of evidence, potential for adverse effects, costs, and patient preferences.

What We Know

- Antihistamines are first-line therapy and effective in the majority of cases of chronic urticaria.
- Higher doses of some second generation antihistamines may be more effective at achieving control of chronic urticaria than typically recommended doses.
- A significant percentage of chronic urticaria patients

- are antihistamine resistant and may require alternative agents for adequate control of their urticaria.
- While the evidence is limited for non-antihistamine therapies in chronic urticaria, a rationale patient-based approach can be developed based on levels and quality of evidence, potential for adverse effects, costs, and patient preferences.

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Atopic Dermatitis

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BACKGROUND

Atopic dermatitis (AD), also known as atopic eczema, is a common inflammatory skin disease that frequently follows a chronic relapsing course. As part of the “atopic triad”, AD often occurs in patients with a personal or family history of asthma or atopic rhinitis. This disease can be lifelong, causing significant interference with school, work, and social interactions.

During the past decade, extraordinary progress has been made in our understanding of the pathogenesis and treatment of AD. Because AD is a complex disease with variable clinical manifestations and no laboratory procedure to provide an unequivocal diagnosis, different sets of criteria have been developed to provide guidance in its diagnosis.

In this chapter, we will review our most recent understanding of the pathogenesis, diagnosis, and treatment of AD.

INTRODUCTION

Atopic dermatitis is an inflammatory skin disease that primarily affects children and young adults. Its lifetime prevalence is approximately 5 to 15% in children from industrialized countries,¹ with approximately 80% of cases starting before the age of 5.² In the United States, the lifetime prevalence in school-aged children has been reported to be up to 17%,³ with prevalence rates increasing in parallel with the rising prevalence of other atopic disorders.⁴

Although the cardinal features of AD are cutaneous hyper-reactivity and hypo-reactivity, as well as intense pruritus that is worse at night, the presentation of AD is often variable because of the differences in age, genetic background, and environmental factors surrounding the individuals studied. One major difference involves the word used to describe the condition, “atopic”. Ironically, many patients do not test positive for common allergens in skin-prick testing or for specific circulating immunoglobulin E (IgE) antibodies in serum testing, and therefore do not present with an atopic form of the disease.⁵ Other subtypes and variations including irritant or allergic contact eczema also exist, but we categorize them all as one condition because the pathogenesis remains unclear.

At this point, there is no consensus on the etiology of atopic dermatitis, but it likely involves some complex interplay between strong genetic and environmental factors; there is only a partial consensus on the diagnosis and treatment of AD.

CLINICAL PICTURE

Atopic dermatitis can be classified into three forms: infantile, childhood, and adult or late-onset. The infantile form is predominantly characterized by acute inflammation with edema, vesicles, exudate and crusting favoring the face, scalp, and extensor surfaces (Figure 13-1). The childhood form tends to be characterized by subacute clinical features such as poorly demarcated erythema and scaling papules and thin plaques, which favor flexural surfaces of the extremities and skin folds including the antecubital fossa, the popliteal fossa, and the neck (Figure 13-2). Of note, periocular erythema, edema and scaling can produce infraorbital lines known as Dennie-Morgan folds (Figure 13-3). The adult, late-onset or chronic form also favors the flexor regions and lesions are typically morphologically characterized by lichenified or fissured plaques, and



FIGURE 13-1 Acute atopic dermatitis. Characterized by acute inflammation with edema, vesicles, exudate and crusting. (From mdconsult.com).



FIGURE 13-2 Subacute atopic dermatitis. Characterized by poorly demarcated erythema and scaling papules and thin plaques. (From ledamod.wordpress.com)

fibrotic papules or nodules from chronic rubbing and scratching (Figure 13-4). Importantly, lesions from any of the three forms can coexist.

MORBIDITY AND COSTS

Compared to other dermatologic diseases, AD can be associated with serious effects on quality of life. Itch and associated sleep loss, social stigmatization from other children and parents, avoidance of activities involving baring of the skin such as swimming, the need for special clothing and bedding, and the need for multiple applications of topical treatments and visits to the dermatologist are just some of the potential causes for morbidity in this patient population.⁶



When direct costs are considered, AD treatment can total \$364 million to \$3.8 billion USD in the United States.⁷ While different study methodologies are responsible for deviations in cost, even the underestimated figures reveal a significant economic burden.^{8,9} For the individual patient, the annual cost is \$338 on average and is almost 1.5-fold higher (\$820) for patients with AD who develop atopic manifestations, such as food allergies, asthma, allergic rhinitis and allergic conjunctivitis.¹⁰ Unfortunately, the high cost of AD is unlikely to diminish in the years to come, especially in light of the increasing prevalence of the disease. To potentially address these costs, more emphasis should be placed on recognizing the disease earlier and implementing therapeutic and preventative measures that reduce the development of atopic manifestations.



FIGURE 13-3 Dennie-Morgan fold: an extra skin fold that develops under the eye plus symmetric excoriated scaly red plaques.



FIGURE 13-4 Chronic atopic dermatitis. Characterized by Lichenified or fissured plaques and fibrotic papules or nodules from chronic rubbing and scratching. (From lookfordiagnosis.com).

GENETICS

The hereditary aspect of AD has long been established. In twin studies, concordance rates for monozygotic twins (23–86%) were higher than dizygotic twins (15–50%).^{11–16} Such a wide range can be explained, in part, by the heterogeneity of phenotypes across studies, and by the environment's role in influencing disease risk and manifestation.

Historically, our understanding of the genetic basis of AD was limited. Until recently, we believed AD to be related to any number of things, such as polymorphisms in the cutaneous mast cell chymase,¹⁷ *Rsal* polymorphisms in the genes coding for the β chain of the high affinity receptor for IgE,¹⁸ and gain of function mutations in the α subunit of the interleukin-4 receptor.¹⁹ Now, after extensive genome-wide linkage studies, association studies and high-throughput expression profiling studies, we better understand the role of skin barrier dysfunction candidate genes in conjunction with innate and adaptive immune response genes in the pathogenesis of AD. To date, more than 100 studies report genetic associations for 81 genes, of which more than half had at least one positive association with AD. Of these, the filaggrin (filament-aggregating protein) gene has been most consistently replicated.²⁰ By binding to keratin fibers in epithelial cells, filaggrin builds a defense matrix of cytoskeleton fibrils in the stratum corneum and a functional barrier at the skin surface. Present in up to 10% of Europeans and North Americans, filaggrin null mutations follow a recessive pattern of inheritance and are associated with mild-to-moderate AD that presents in childhood.^{21,22} Deficiency results in a compromised skin barrier that fails to protect against microbial insults and antigens, which in turn predisposes afflicted individuals to allergic sensitization, allergic rhinitis, and atopic dermatitis. AD patients with the filaggrin mutation also present with disease that is of earlier onset, more severe in nature, more persistent in course, and are more likely to develop asthma and allergic sensitizations.²³

Although recent research has argued that the primary defect in AD resides in the epidermal barrier,²⁴ it is important to recognize that a significant number of patients with AD do not have any known filaggrin gene mutation and approximately 40% of patients with the filaggrin null mutation do not have AD.²⁵ Thus, despite our progress in better understanding the genetics of AD, we have yet to discover the exact relationship between barrier dysfunction and immune dysregulation in patients with AD. Current research identifying other skin barrier proteins that are essential for normal barrier function as well as specific biomarkers for AD will likely further elucidate the drivers of this disease.

Also worth noting, parent-of-origin effects, or maternal hereditability, has also been linked to AD and supported by genetic association studies with maternally transmitted alleles in the kazal-type serine protease inhibitor 5 (SPINK5) gene.^{26–28}

ENVIRONMENT

There has been a large increase in the prevalence of atopic dermatitis over the past 30 years.²⁹ It has been shown that members of wealthier families are more frequently affected.³⁰ The implications of this are unclear but may be related to greater exposure to indoor allergens. According to the “hygiene hypothesis,” children born into larger families express less atopy because of frequent exposure to infections, presumably from their siblings.³¹ However, a population-based cross-sectional study of 12,601 children between the ages of 5–7 and 9–11 from Germany found that factors such as day-care attendance and the number of older siblings were not associated with a decreased risk of developing AD.³²

Exposure to allergens, such as dust-mites, is thought to play a role in AD.³³ Interestingly, despite popular belief that furry pets kept at home are responsible for the development of AD in children, a systematic review of cohort, case control and cross-sectional studies by Langan et al. found evidence to suggest protective effects from the exposure.³⁴ Exposure to other irritants, such as bacteria, is likely to be an equally important risk factor.³⁵

Other studies favoring the role of environmental factors in the pathogenesis of AD include studies involving migrants. One study showed that 14.9% of black Caribbean children living in London developed AD compared to only 5.6% of similar children living in Kingston, Jamaica.³⁶

Psychosocial factors early in life also appear to play a role. In a systematic review of 43 cohort studies, Chida et al. found evidence to suggest a positive correlation between adverse psychosocial factors and future atopic disorder. More notably, the subgroup meta-analysis on the healthy and atopic disorder patient populations showed psychosocial factors had both an etiologic and prognostic effect on atopic disorders.³⁷

Still, many of the environmental risk factors are not fully understood at this time and the fact that many cases of atopic dermatitis spontaneously improve around the time of puberty further complicates this issue.

IMMUNOBIOLOGY

As previously discussed, the fundamental lesion in AD is a defective skin barrier that results in dry skin. Entry of irritants and microbes stimulates both the innate and adaptive immune systems which in turn contribute to the overall inflammatory process in AD.

Any initiating stimulus such as mechanical trauma secondary to scratching can potentially stimulate the local production of proinflammatory cytokines including interleukin 1 (IL-1) and tumor necrosis factor alpha (TNF alpha) as well as chemokines that allow trafficking of leukocytes into the skin.^{38–42}

Overall, the dysregulated cytokine profile in AD patients favors a CD4+ Th2 response with the predominant production of Th2 cytokines IL-4, IL-5 and IL-13.⁴³ These cytokines,

specifically IL-4, are involved in IgE isotype switching in B cells which allows subsequent binding of allergens to IgE receptors on mast and dendritic cells and stimulation of a local immune response. Interestingly, recent observations seem to indicate that in contrast to acute AD lesion which contain a Th2 predominant subset of cells, chronic lesions may contain either both the Th2 and Th1 subset of cells or a predominantly Th1 subset of cells.^{44–46}

Patients with AD are also known to be more susceptible to microbial infections, particularly with *S. aureus*. Studies have shown that the presence of antimicrobial peptides is significantly decreased in acute and chronic AD lesions and this may contribute to the increased susceptibility of AD patients to skin colonization and infection. Exposure to microbial superantigens and toxins then allows worsening of skin inflammation.^{47,48}

Further research and a better understanding of the complex immunology behind AD may allow for improvements in treatment and care of patients with this disease.

DIAGNOSTIC CRITERIA

Atopic dermatitis has a wide spectrum of dermatologic manifestations. With no specific diagnostic tests available, the diagnosis of AD is clinical. Over the years, numerous sets of diagnostic criteria have been suggested. The first set introduced by Hanifin and Rajka in 1980 consisted of 4 major and 23 minor criteria.⁵⁵ Despite the criteria being quoted in hundreds of scientific studies, only two validation studies have been published, and these found the model to be of low specificity (78–94%), time consuming and unmanageable.⁵⁶ As a refinement of Hanifin and Rajka's diagnostic criteria, the UK diagnostic criteria was introduced by Williams et al. in 1997.⁵⁷

Based on a systematic review of 27 published validation studies of various diagnostic criteria for AD, the UK diagnostic criteria was found to be the most extensively validated, with a sensitivity ranging from 10 to 100% and a specificity ranging from 89 to 99%. The markedly low sensitivity of 10% was reported by an independent Iranian study by Firooz et al. and is likely due to international differences in clinical phenotype, environmental factors, and observation bias.⁵⁸

Although most healthcare professionals do not use diagnostic criteria in routine practice, the simplified UK Working Party criteria (Table 13-1) can be useful in difficult cases and for conducting clinical trials. The criteria are all noninvasive and consist of one mandatory criterion and five major criteria, of which three have to be present for diagnosis.

To date, 20 different scales have been identified to measure disease severity. Based on a systematic review conducted by Schmitt et al. only 3 scales, SCORing Atopic Dermatitis (SCORAD), the Eczema Area and Severity Index (EASI), and the Patient Oriented Eczema Measure (POEM) have been sufficiently tested and found to perform adequately.⁵⁹ Of the three, POEM is considered

TABLE 13-1—The UK Working Party Diagnostic Criteria for Atopic Dermatitis

Must have:

- An itchy skin condition in the past 12 months

Plus three or more of the following:

- Previous involvement of skin creases (i.e., bends of elbows)
- Personal history of asthma or hay fever (or history of atopic disease in first degree relative if child is >4 years)
- History of general dry skin in the past 12 months
- Onset before the age of 2 years (not used if child aged <4 years)
- Visible flexural dermatitis (including dermatitis affecting cheeks or forehead and outer areas of limbs in children aged <4 years)

Williams, HC, Burney, PGJ, Hay, RJ, et al: The U.K. Working Party's diagnostic criteria for atopic dermatitis I. derivation of a minimum set of discriminators for atopic dermatitis. *Br J Dermatol* 1994;131: 383–396.

the most practical measure of patient outcome in the clinic. It consists of seven questions on subjective symptoms and disease severity and can be easily filled out by the patient prior to being seen by the physician.

TREATMENT

Few clinical trials evaluate the management of AD beyond 6 weeks duration, which may not be sufficient time to gauge the long-term outcomes of modern treatment modalities.⁶⁰ Without long-term studies, it is difficult to determine whether modern treatments have any effect on the chronic nature of the disease. Thus, the general approach to treatment of AD has been to focus on short-term control of symptoms by using conservative measures that emphasize the elimination of exacerbating factors, provide symptomatic relief and minimize exposure to potentially toxic drugs (see Table 13-2). For cases of severe refractory disease that fail to respond to conventional therapy, second-line treatments such as phototherapy or immunosuppressive medications may be considered. In all cases, it is crucial to provide patients with information about their disease and to address their questions and concerns.

It is important to help patients eliminate factors that may be responsible for exacerbating their disease.⁶¹ Such factors may include excessive bathing, low humidity, emotional stress, xerosis, infections, and exposure to fragrances, solvents, detergents, house dust, and wool.⁶² For patients experiencing significant stress or psychosocial disturbances, psychologic services can be offered.³⁷

To address the issue of xerosis, skin hydration is critical. While lotions with high water and low oil content can induce evaporation, thick creams with low water content or ointments with zero water content, offer better protection against xerosis. Different preparations, including water-in-oil (e.g., Eucerin[®]), oil-in-water (e.g., Moisturel[®]), urea based (e.g., Laceran[®]) and glycerin based preparations, have been proven effective in improving clinical

TABLE 13-2—Major Treatment Modalities

	Indication(s)	Routine Dose(s)	Strength of Recommendation*	Level of Evidence**
Noninflamed Skin				
Emollients	Xerosis, Pruritus	Multiple times daily, especially after bathing	A	Good
Hydrogels	Xerosis, Pruritus	Twice daily	A	Fair
Antihistamines	Sedation, Pruritus	Nightly	B	Fair
Inflamed Skin				
Topical Corticosteroids	Irritation, Pruritus	Daily to twice daily	A	Good
Topical Calcineurin Inhibitors	Refractory to topical steroids; thin-sensitive, steroid sparing skin	Twice daily	A	Good
Systemic Steroids	Acute flare	Short burst with tapering over few weeks	A	Fair
Systemic Calcineurin Inhibitors	Refractory	Not available	D	Poor
Cyclosporine	Refractory	Short course of 3–4 mg/kg daily	B	Good
Other Immunosuppressants	Refractory	Not available	B	Poor
Biologics	Refractory	Not available	I	Poor
Phototherapy	Refractory	Average 3 times per week	B	Fair
Infected Skin				
Bleach Baths	Reduce colonization	Several times weekly to daily	B	Poor
Mupirocin	Local infection	2–3 times daily for 5 days	A	Good
Gentian violet	Local infection	Not available	D	Fair
Chlorhexidine	Local infection	Not available	D	Fair
Oral Antibiotics	Widespread Infection	Depends on pathogen and appropriate antibiotic	A	Good
Antivirals	Herpes Simplex Infection	Topical: 6 times daily for 7 days; oral: dosing depends on antiviral agent used	A	Good
Antifungals	Candida or Dermatophyte Infection	Twice daily	A	Good

*Strength of recommendations is based on the U.S. Preventative Services Task Force (USPSTF) criteria for grading recommendations. The five classifications (A, B, D, I) reflect the strength of evidence and magnitude of net benefit.

A- Strongly recommends that clinicians provide [the service] to eligible patients.

B- No recommendation for or against routine provision of (the service).

D- Recommends against routinely providing (the service) to asymptomatic patients.

I- Insufficient evidence to recommend for or against routinely providing (the service).

**Level of Evidence is based on the USPSTF criteria for grading the quality of evidence for a service and consists of a 3-point scale (good, fair, poor).

Good: Evidence includes consistent results from well-designed, well-conducted studies in representative populations that directly assess effects on health outcomes.

Fair: Evidence is sufficient to determine effects on health outcomes, but the strength of the evidence is limited by the number, quality, or consistency of the individual studies, generalizability to routine practice, or indirect nature of the evidence on health outcomes.

Poor: Evidence is insufficient to assess the effects on health outcomes because of limited number or power of studies, important flaws in their design or conduct, gaps in the chain of evidence, or lack of information on important health outcomes.

symptoms of AD as both primary and adjunctive therapy for AD; however, no systematic review comparing their efficacies is available.^{63–68} In general, emollients have been

associated with few adverse events and are limited to a few reports of burning upon application.⁶⁹ Alternatively, medical devices, known as hydrogels, can also be used to retain

moisture and provide a mechanical barrier to irritants. These FDA-approved, prescriptive treatments, including MimyX cream[®],⁷⁰ EpiCeram[®]⁷¹ and Atopiclair Nonsteroidal Cream[®],⁷² are indicated to improve xerosis and manage the burning and itching associated with AD. In a recent clinical trial involving 113 children with moderate to severe AD, EpiCeram was shown to be comparable to mid-strength topical corticosteroid in improving xerosis and managing the burning and itching associated with AD.⁷³ Furthermore, these agents are not associated with any of the undesirable side effects and usage restrictions associated with topical steroids. Drugs with antihistaminic effects can be tried to suppress pruritus, prevent exacerbation caused by scratching and improve sleep (especially if sedating) in patients with AD, however placebo-controlled studies concerning their antipruritic effects show conflicting results.⁷⁴⁻⁷⁹ One explanation for these variations is that histamine is only one of several mediators of pruritus^{86,87} and many different nociceptive mechanisms are involved in AD.^{88,89}

Another explanation is that most of these studies are limited to investigation of the role of histamine H1 antihistamines in the treatment of pruritus. In a more recent study conducted by Reese, et al.⁹² histamine was shown to generate itch in mice via the H1, H4, and possibly H3 receptors. Interestingly, the histamine H2 receptor does not seem to be involved in pruritus as the H2 receptor agonist Dimaprit did not induce dose-dependent scratching, and the H2 antagonist Cimetidine did not significantly reduce histamine-induced scratching. To further investigate the relative contribution of the four known histamine receptors, Thurmond et al.⁹³ used selective antagonists in mice models and found the H4 receptor blockers most effective in inhibiting itch. Similarly, Wolfgang Bäumer et al.⁹⁴ found that compared to administering the H1 receptor antagonist Cetirizine alone, a combination of H1 and H4 receptor antagonists resulted in greater inhibition of scratching behavior associated with allergic dermatitis in mice. Although preliminary, these studies suggest a new strategy using H4, and possibly H3, receptor blockers to treat pruritus in AD. However, before any recommendations can be made, further research supporting their efficacies and safety in humans must be conducted.

As previously mentioned, patients with AD have an increased risk for cutaneous bacterial, viral, and fungal infections. These secondary infections exacerbate the disease and should be treated if suspected. Infection with *Staphylococcus aureus* (*S. aureus*) is most common and presents with honey-colored crusting, folliculitis, and pyoderma (Figure 13-5). Local infections can be treated with topical mupirocin (Bactroban[®]) applied 2–3 times daily for 5 days, while more extensive disease may require oral antibiotics.⁹⁵ In any case, all infections should be cultured and treated with the appropriate antimicrobial agent.

Patients with AD also show higher rates of *S. aureus* colonization (76–100%) compared to healthy control subjects (2–25%).^{96,97} For this reason, many researchers



FIGURE 13-5 Secondary Infection with *Staphylococcus aureus* is characterized by honey-colored, crusting, folliculitis and pyoderma.

have investigated the role of bacterial growth suppression in the treatment for AD. Although two reports suggest that topical antibiotic application to all atopic areas could improve clinical severity,^{98,99} more recent studies do not show any improvement.^{100,101} These studies also show that adjunctive application of topical mupirocin or fusidic acid to corticosteroid therapy does not decrease clinical severity of atopic lesions more significantly than topical corticosteroid administration alone. In contrast, gentian violet and chlorohemin have been found to decrease *S. aureus* density and improve AD.^{102,103} However, the use of either agent is generally limited by the former's cosmetic side-effects and the latter's link to irritant contact dermatitis when used extensively. Alternatively, chronic use of diluted bleach baths with intermittent intranasal application of mupirocin ointment have activity against *S. aureus*, including MRSA, and have been shown to significantly improve the severity of AD and reduce the frequency of skin infections.¹⁰⁴

Secondary infection with herpes simplex, known as eczema herpeticum, also occurs commonly and is characterized by vesicles, punched out erosions and hemorrhagic crusting (Figure 13-6). Patients should be treated immediately with oral antiviral therapy. Likewise, dermatophyte infections are seen more commonly in patients with AD and can be treated with standard regimens of topical or oral antifungals.

Topical corticosteroids are the mainstay of therapy for AD. The strength and vehicle of choice depend on the severity of the disease. Most trials of topical steroids are short in duration and fail to address how long the patient should continue therapy. In addressing the issue of frequency of application, two systematic reviews suggested once rather than twice daily treatment as the first step in the management of all patients with atopic dermatitis.^{63,105}

Commonly reported adverse effects of topical corticosteroid use include stinging, burning, contact dermatitis, pruritus, dryness, folliculitis, excess hair growth



FIGURE 13-6 Secondary infection with herpes simplex is characterized by vesicles, punched out erosions and hemorrhagic crusting.

and pigment alteration. More concerning adverse events include skin atrophy and suppression of the hypothalamic-pituitary-adrenal (HPA) axis. Suppression of the HPA axis is rare and tends to occur in patients receiving potent topical preparations in combination with inhaled glucocorticoids for their concurrent asthma.^{106,107} Again, most studies have been too short to sufficiently address the risk of long-term use of topical steroids.

Moreover, there are no trials that compare all contenders for the most effective and safe topical corticosteroid. However, two newer topical corticosteroids, desonide gel (0.05%) and fluticasone propionate (0.05%), have emerged with treatment efficacies comparable to other topical corticosteroids associated with greater side effects.^{108,109} In addition, fluticasone propionate cream (0.05%) has a unique quality of not being associated with skin thinning, which may in part be caused by its minimal subcutaneous penetration, rapid metabolism and/or its high binding capacity for the glucocorticoid receptor.^{110,111}

Systemic corticosteroids are rarely used to treat AD long-term, but their short-term use to treat severe flare-ups is of common practice.¹¹² Two randomized-controlled trials have evaluated the efficacy and safety of systemic corticosteroids. The first study evaluated the administration of 4 weeks daily oral beclomethasone 0.8 mg/kg plus nasal beclomethasone 0.4 mg/kg to 26 children suffering refractory AD, and found a 22% reduction in disease severity and reported no adverse events.¹¹³ Similarly, the second study treated patients with flunisolide at age-adjusted doses for 2 weeks and showed an average 39% decrease in clinical severity, no relapses for 3 weeks after discontinuation of the medication, and no adverse events.¹¹⁴ Unfortunately, data from these trials is insufficient to draw any definite conclusions regarding the safety of systemic corticosteroids. Thus, most guidelines, including the 2006 Practical Allergy (PRACTALL) consensus group guidelines,¹¹⁵ agree that in the case of acute flares, patients might benefit from a short

course of systemic corticosteroids, but that long-term use and administration to children should be avoided.

As a second-line therapy, topical calcineurin inhibitors (tacrolimus and pimecrolimus) have been shown to be as effective as low potency topical steroids in the treatment of moderate-to-severe AD.^{116,117} Moreover, unlike topical corticosteroids, topical calcineurin inhibitors do not cause skin atrophy and are therefore particularly useful in patients with facial, neck, and skin fold involvement. Tacrolimus and pimecrolimus both work by inhibiting cytokine production. In addition, tacrolimus causes an alteration in the epidermal antigen-presenting dendritic cells that decreases immunologic responses to antigens.¹¹⁸ Studies comparing these two calcineurin inhibitors found that tacrolimus ointment may be more effective than pimecrolimus cream but that it may also cause greater local irritation.¹¹⁹

In 2006, the FDA issued a public health warning and labeling change for topical calcineurin inhibitors to inform patients and providers about their potential malignancy risk.¹²⁰ Although data from several case reports and animal studies suggested a possible link between these agents and different lymphomas and skin cancers, a recent propensity-score-matched cohort study found no increase in the incidence of lymphoma among topical pimecrolimus or topical tacrolimus users relative to corticosteroid users at an average of 1.3 years follow-up. This study is useful in that immunosuppression-related lymphoma typically develops within 2 years of exposure. Unfortunately, this study does not address the potential risk that may be associated with longer-term exposures to these drugs and fails to draw any firm conclusions about the pediatric populations. Likewise, another recent retrospective cohort observational study showed no increase in the overall cancer rate of topical calcineurin users versus nonusers, but did associate the use of topical tacrolimus with an increased risk of T-cell lymphoma.¹²¹ Without long-term studies fully evaluating the safety of these topical agents, the FDA recommends limiting their use to patients unresponsive to or intolerant of other treatments, and prohibits their use in children less than 2 years of age. Similarly, oral calcineurin inhibitors have been shown to be effective in refractory cases of AD but are generally avoided because of their potentially toxic side effect profiles.¹²³

Immunosuppressants (e.g., cyclosporine, methotrexate, azathioprine, and mycophenolate mofetil) are other systemic agents that can be used conservatively in the treatment of refractory disease. In evaluating the use of cyclosporine in the treatment of severe AD, a randomized, open-label, 12-month study showed that treatment at a starting dose of 3 mg/kg/day was efficacious, well tolerated, and associated with only a few side effects such as an increase in serum creatinine and diastolic blood pressure.¹²⁴ Other studies have shown that patients typically demonstrate a clinical response within 10–20 days after beginning treatment,^{125,126} and that in most patients treatment can be tapered slowly after 8 weeks.¹²⁷ However, in a

randomized comparison in 40 children, Harper et al. found that relative to multiple short-term (12 weeks) courses of therapy, continuous therapy with cyclosporine for 1 year resulted in more consistent control of symptoms and more significant improvement of quality of life from baseline.¹²⁸ Based on these and similar studies, the American Academy of Dermatology recommends the use of cyclosporine for the treatment of severe and refractory AD even though it is not currently approved by the FDA for this indication.¹²⁹

Methotrexate, a very effective agent used in the treatment of chronic inflammatory conditions such as psoriasis and rheumatoid arthritis, has also been reported to be effective in the treatment of AD by a number of anecdotal reports and small retrospective studies.¹³⁰⁻¹³² In a three year prospective study conducted by Bergman et al. nine patients unresponsive to prolonged therapy with oral antihistamines and local corticosteroids were administered low dose (10–20 mg) methotrexate therapy once a week along with folic acid supplements. Of the nine participants, six patients achieved complete remission after 3 months of therapy and three showed significant improvement. Initial response was noted after 3 to 7 weeks and no serious adverse events were noted during treatment.¹³³

In addition, data from case reports, retrospective studies and a few small clinical trials support the use of mycophenolate mofetil, a purine biosynthesis inhibitor indicated for the prophylaxis of organ rejection, and azathioprine, a DNA and RNA biosynthesis inhibitor with immunosuppressant and cytotoxic actions, in refractory cases of AD.¹³⁴⁻¹³⁹ Like oral calcineurin inhibitors, systemic immunosuppressants can be used in cases of severe and refractory AD, but their long-term use should be avoided.

More recently, a few case reports and trials have documented the use of biologics in the treatment of AD. Omalizumab, rituximab, infliximab, alefacept, etanercept, efalizumab, interferon gamma and mepolizumab have all been administered to patients with AD but have shown inconsistent results. Of note, efalizumab was taken off the market because of reports associating its use with

progressive multifocal leukoencephalopathy. Given the side effect profiles of the remaining drugs, further studies are necessary before any of them can be routinely recommended for the treatment of AD.¹⁴¹⁻¹⁵⁶

Another second-line therapy is phototherapy with broadband UVB, UVA, narrowband UVB, or psoralen plus UVA (PUVA).¹⁵⁷⁻¹⁵⁹ Some studies suggest that narrowband UVB and UVA-1 may be more efficacious than the other modalities.¹⁶⁰⁻¹⁶² In a study of thirty-two patients receiving UVA1 irradiation 5 times per week for 3 consecutive weeks, Ring et al. validated the efficacy of UVA-1 phototherapy in decreasing disease severity but concluded that the effectiveness was short-term and unsustainable three months after discontinuation of treatment.¹⁶³ Furthermore, the general use of phototherapy is limited to severe and refractory cases because of its potential association with an increased risk of skin cancer.¹⁶⁴⁻¹⁷⁶

PROGNOSIS

Approximately 60% of childhood patients are disease free by early adolescence, however many of these cases are likely to see recurrence of their disease, often in the form of hand eczema, in adulthood.¹⁷⁷ Factors most consistently predicting persistent atopic dermatitis include early onset, severe widespread disease in infancy, concomitant asthma or hay fever and a family history of atopic dermatitis. Psychosocial factors also influence the prognosis of atopic disorder and should therefore be addressed in the management of the disease.³⁷

CONCLUSION

AD is a common inflammatory skin disease that negatively impacts the quality of life of those affected and produces a significant economic burden on society. This review has attempted to provide key features of our understanding of the etiology, diagnosis, and treatment of atopic dermatitis (Table 13-3). AD remains primarily a clinically based

What We Know

- Atopic Dermatitis (AD) is a common inflammatory skin disease that frequently follows a chronic relapsing course.
- It negatively impacts quality of life and produces a significant economic burden.
- As part of the “atopic triad”, AD often occurs in patients with a personal or family history of asthma or atopic rhinitis.
- There is no consensus on the etiology of AD, but it likely involves a relationship between skin barrier dysfunction and immune dysregulation caused by both genetic and environmental factors.
- Its presentations are variable and influenced by differences in age, genetic background, and environmental factors.

- With no specific diagnostic tests available, the diagnosis of AD is clinical.
- Topical corticosteroids are generally considered first line treatment of mild to moderate AD; there is only a partial consensus on the treatment of severe or recalcitrant AD.
- Patients with AD are known to be more susceptible to microbial infections, particularly with *S. aureus*, and should be treated accordingly.
- Preventive measures are recommended and include skin hydration as well as avoidance of triggers and exacerbating factors.

TABLE 13-3—Systematic Reviews on Atopic Dermatitis

Treatment(s)		
Publication	Number of studies	Finding(s)
Fleischer AB, Boguniewicz M. An approach to pruritus in atopic dermatitis: a critical systematic review of the tacrolimus ointment literature. <i>J Drugs Dermatol.</i> 2010;9(5):488–98.	52	(1) Tacrolimus is more effective at reducing pruritus when compared with pimecrolimus and some topical corticosteroids. (2) It is safer for long term use when compared with topical corticosteroids.
El-Batawy MM, Bosseila MA, Mashaly HM, et al. Topical calcineurin inhibitors in atopic dermatitis: a systematic review and meta-analysis. <i>J Dermatolog Sci.</i> 2009;54(2):76–87.	19	(1) Topical calcineurin inhibitors (TCI) in AD are more effective than placebo. (2) Although less effective than topical corticosteroids (TCS), pimecrolimus has its value in long-term maintenance and as a steroid-sparing agent. (3) In treatment of moderate to severe AD, topical tacrolimus is as effective as moderately potent TCs, and more effective than mild preparations. (4) Chronic AD lesions of the face and flexures are the most justified indication for topical calcineurin inhibitors.
Meduri NB, Vandergriff T, Rasmussen H, et al. Phototherapy in the management of atopic dermatitis: a systematic review. <i>Photodermatology, Photoimmunology & Photomedicine.</i> 2007;23(4):106–12.	9	(1) Phototherapy with medium-dose (50 J/cm ²) UVA1, if available, should be used to control acute flares of AD. (2) UVB modalities, specifically narrow-band UVB, should be used for the management of chronic AD.
Chida Y, Steptoe A, Hirakawa N, et al. The effects of psychologic intervention on atopic dermatitis. A systematic review and meta-analysis. <i>Int Arch Allergy and Immunol.</i> 2007;144(1):1–9	8	(1) Meta-analysis revealed that psychologic interventions had a significant ameliorating effect on eczema severity, itching intensity and scratching in atopic dermatitis patients.
Schmitt J, Schmitt N, Meurer M. Cyclosporin in the treatment of patients with atopic eczema - a systematic review and meta-analysis. <i>J Eur Acad Dermatol Venereol.</i> 2007;21(5):606–19.	15	(1) Effectiveness of cyclosporin is similar in adults and children, but tolerability might be better in children. (2) As data to adequately evaluate the long-term effectiveness and safety of cyclosporin in patients with atopic eczema are unavailable, long-term registries are encouraged.
Schmitt J, Schkel K, Schmitt N, et al. Systemic treatment of severe atopic eczema: a systematic review. <i>Acta Dermato-Venereologica.</i> 2007;87(2):100–11.	27	(1) Cyclosporine is recommended as first option for patients with atopic eczema refractory to conventional treatment. (2) Evidence from randomized controlled trials also exists for interferon-? and azathioprine. (3) Systemic glucocorticosteroids have not been assessed adequately in studies. (4) Mycophenolate mofetil showed effectiveness in 2 small-uncontrolled studies. (5) Intravenous immunoglobulins and infliximab are not recommended based on published data.
Callen J, Chamlin S, Eichenfield L F, et al. A systematic review of the safety of topical therapies for atopic dermatitis. <i>Br J Dermatol.</i> 2007;156(2):203–21.	61	Physiological changes appear to be uncommon and systemic complications rare and have only been found with use of topical corticosteroids.
Langan SM, Thomas KS, Williams HC. What is meant by a “flare” in atopic dermatitis? A systematic review and proposal. <i>Arch Dermatol.</i> 2006;142(9):1190–6.	15	A flare of AD is defined as an episode requiring escalation of treatment or seeking additional medical advice. Consideration should also be given to totally controlled weeks and well-controlled weeks to assess overall disease activity in patients with AD.
Garside R, Stein K, Castelnovo E, et al. The effectiveness and cost-effectiveness of pimecrolimus and tacrolimus for atopic eczema: a systematic review and economic evaluation. <i>Health Technology Assessment.</i> 2005;9(29):iii, xi-xiii,1.	18	(1) Pimecrolimus is more effective than placebo treatment in controlling mild to moderate atopic eczema. (2) Tacrolimus is more effective than the placebo treatment and mild topical corticosteroids. (3) No significant difference shown when compared to topical corticosteroids. (4) Short-term adverse effects with both immunosuppressants are relatively common, but appear to be mild. (5) Experience of long-term use of the agents is lacking so the risk of rare but serious adverse effects remains unknown. (6) No conclusions can be confidently drawn about the cost-effectiveness of pimecrolimus or tacrolimus compared to active topical corticosteroid comparators.

Continued

TABLE 13-3—Systematic Reviews on Atopic Dermatitis (Continued)

Treatment(s)		
Publication	Number of studies	Finding(s)
Ashcroft DM, Dimmock P, Garside R, et al. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized-controlled trials. <i>BMJ</i> . 2005;330(7490):516.	25	(1) Both topical pimecrolimus and topical tacrolimus are more effective than placebo treatments for atopic dermatitis, but in the absence of studies that show long-term safety gains, any advantage over topical corticosteroids is unclear. (2) Topical tacrolimus is similar to potent topical corticosteroids and may have a place for long term use in patients with resistant atopic dermatitis on sites where side effects from topical corticosteroids might develop quickly.
Green C, Colquitt JL, Kirby J, et al. Topical corticosteroids for atopic eczema: clinical and cost effectiveness of once-daily vs. more frequent use. <i>Br J Dermatol</i> . 2005;152(1):130–41.	10	(1) No clear differences in outcomes between once-daily and more frequent application of topical corticosteroids.
Green C, Colquitt JL, Kirby J, et al. Clinical and cost-effectiveness of once-daily versus more frequent use of same potency topical corticosteroids for atopic eczema: a systematic review and economic evaluation. <i>Health Technology Assessment</i> . 2004;8(47):1–120.	10	(1) Clinical effectiveness of once-daily and more frequent application of potent topical corticosteroids is very similar, but it does not offer a basis for favoring either option. (2) The cost-effectiveness of once daily versus more frequent use will depend on the generalizability of the findings to the specific treatment decision and the relative product prices.
Hoare C, Li Wan Po A, Williams, H. Systematic review of treatments for atopic eczema. <i>Health Technology Assessment</i> . 2000;4(37):1–191.	272	(2) There was reasonable RCT evidence to support the use of oral cyclosporin, topical corticosteroids, psychologic approaches and ultraviolet light therapy. (2)There was insufficient evidence to make recommendations on maternal allergen avoidance for disease prevention, oral antihistamines, Chinese herbs, dietary restriction in established atopic eczema, homeopathy, house dust mite reduction, massage therapy, hypnotherapy, evening primrose oil, emollients, topical coal tar and topical doxepin. (3) There was no RCT evidence to support any clear clinical benefit on the use of avoidance of enzyme washing powders, cotton clothing as opposed to soft-weave synthetics, biofeedback, twice-daily as opposed to once-daily topical corticosteroids, topical antibiotic/steroid combinations versus topical steroids alone and antiseptic bath additives. (4) There was complete absence of RCT evidence on short bursts of potent versus longer-term weaker topical steroids, dilution of topical corticosteroids, oral prednisolone and azathioprine, salt baths, or impregnated bandages, wet-wrap bandages, water softening devices, allergy testing, and different approaches to organization of care.
Prevention		
Publication	Number of studies	Finding(s)
Alexander D, Schmitt DF, Tran N L, et al. Partially hydrolyzed 100% whey protein infant formula and atopic dermatitis risk reduction: a systematic review of the literature. <i>Nutrition Reviews</i> . 2010;68(4):232–45.	18	All studies reported a reduced incidence of AD was observed in the PHF-W group compared with the intact protein cow's milk group.

Prevention		
Publication	Number of studies	Finding(s)
Kremmyda L, Vlachava M, Noakes PS, et al. Atopy Risk in Infants and Children in Relation to Early Exposure to Fish, Oily Fish, or Long-Chain Omega-3 Fatty Acids: A Systematic Review. <i>Clin Rev in Allergy & Immunol.</i> 2009.	29	(1) Majority of studies showed a protective effect of fish intake during infancy and childhood on atopic outcomes. (2) The provision of fish oil during pregnancy may reduce sensitization to common food allergens and reduce prevalence and severity of atopic dermatitis in the first year of life, with a possible persistence until adolescence. (3) Supplementation in infancy may decrease the risk of developing some manifestations of allergic disease, but this benefit may not persist as other factors come into play. (4) It is not clear whether fish oil can be used to treat children with asthma.
Anandan C, Nurmatov U, Sheikh, A. Omega 3 and 6 oils for primary prevention of allergic disease: systematic review and meta-analysis. <i>Allergy.</i> 2009;64(6):840–8.	10	Supplementation with omega 3 and omega 6 oils is unlikely to play an important role as a strategy for the primary prevention of sensitization or allergic disease.
Yang YW, Tsai CL, Lu, CY. Exclusive breastfeeding and incident atopic dermatitis in childhood: a systematic review and meta-analysis of prospective cohort studies. <i>Br J Dermatol.</i> 2009;161(2):373–83.	21	No strong evidence of a protective effect of exclusive breastfeeding for at least 3 months against AD, even among children with a positive family history.
Bath-Hextall F, Delamere FM, Williams H C. Dietary exclusions for improving established atopic eczema in adults and children: systematic review. <i>Allergy.</i> 2009;64(2):258–64.	9	(1) No benefit of an egg- and milk-free diet in unselected participants with atopic eczema. (2) No evidence of benefit in the use of an elemental or few-foods diet in unselected cases of atopic eczema. (3) There may be some benefit in using an egg-free diet in infants with suspected egg allergy who have positive specific IgE to eggs.
Chida Y, Hamer M, Steptoe A. A bidirectional relationship between psychosocial factors and atopic disorders: a systematic review and meta-analysis. <i>Psychosomatic Med.</i> 2008;70(1):102–16.	43	(1) A robust relationship between psychosocial factors and atopic disorders exists. (2) Findings support the use of psychological in addition to conventional physical and pharmacologic interventions, in the successful prevention and management of atopic disorders.
Gdalevich M, Mimouni D, David M, et al. Breast-feeding and the onset of atopic dermatitis in childhood: a systematic review and meta-analysis of prospective studies. <i>J Am Acad Dermatol.</i> 2001;45(4):520–7.	18	(1) Exclusive breast-feeding during the first 3 months of life is associated with lower incidence rates of atopic dermatitis during childhood in children with a family history of atopy. (2) This effect is lessened in the general population and negligible in children without first-order atopic relatives.
Pathogenesis		
Publication	Number of studies	Finding(s)
Van den Oord RA, Sheikh A. Filaggrin gene defects and risk of developing allergic sensitization and allergic disorders: systematic review and meta-analysis. <i>Br Med J. (Clinical research ed.)</i> 2009;339:b2433.	24	Filaggrin gene defects increase the risk of developing allergic sensitization, atopic eczema, and allergic rhinitis
Health Economics		
Publication	Number of studies	Finding(s)
Mancini AJ, Kaulback K, Chamlin, SL. The socioeconomic impact of atopic dermatitis in the United States: a systematic review. <i>Pediatric Dermatol.</i> 2008;25(1):1–6.	4	(1) National cost estimates ranged widely, from \$364 million to \$3.8 billion US dollars per year. (2) The cost of atopic dermatitis is significant and will likely increase in proportion to increasing disease prevalence. (3) Measurement of the cost of atopic dermatitis in the United States has been limited to direct cost-identification analyses, with few studies measuring the indirect cost of disease.

Continued

TABLE 13-3—Systematic Reviews on Atopic Dermatitis (Continued)

Diagnosis		
Publication	Number of studies	Finding(s)
Brenninkmeijer EEA, Schram ME, Leeflang MMG, et al. Diagnostic criteria for atopic dermatitis: a systematic review. <i>Br J Dermatol.</i> 2008;158(4):754–65.	27	(1) The U.K. diagnostic criteria are the most extensively validated. (2) Improvement of methodologic design for validation studies and uniformity in well-validated and applicable diagnostic criteria are needed to improve future intervention studies and to compare study results.
Outcome Measure		
Schmitt J, Langan S, Williams HC. What are the best outcome measurements for atopic eczema? A systematic review. <i>J Allergy Clin Immunol.</i> 2007;120(6):1389–98.	20	(1) There is adequate construct validity for 3 measurements (Severity Scoring of Atopic Dermatitis index [SCORAD], Eczema Area and Severity Index [EASI], and Three Item Severity Score), adequate internal consistency of 1 scale (Patient-oriented Eczema Measure [POEM]), adequate interobserver reliability of 5 measurements (Basic Clinical Scoring System; Nottingham Eczema Severity Score; Objective Severity Assessment of Atopic Dermatitis; Six Area, Six Sign Atopic Dermatitis severity score; and SCORAD), adequate test-retest reliability of 1 scale (POEM), and adequate sensitivity to change of 3 measurements (EASI, SCORAD, and Investigators' Global Atopic Dermatitis Assessment). (2) Most outcome measurements have adequate content validity, as assessed by patients and experts. (3) Only SCORAD, EASI, and POEM have been tested sufficiently on time to perform the assessment and performed adequately.
Terminology		
Langan SM, Thomas KS, Williams HC. What is meant by a “flare” in atopic dermatitis? A systematic review and proposal. <i>Arch Dermatol.</i> 2006;142(9):1190–6.	15	A flare of AD is defined as an episode requiring escalation of treatment or seeking additional medical advice. Consideration should also be given to totally controlled weeks and well-controlled weeks to assess overall disease activity in patients with AD.

diagnosis. Fortunately, with the use of currently available treatment options, most cases of AD can be successfully controlled. In time, an improved understanding of the genetic and immunologic basis of AD will provide further opportunities for the development of more effective therapies.

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Treatment of Melasma

14

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SUMMARY

Melasma is one of the most common hyperpigmentation disorders, primarily affecting women of reproductive age. It tends to be more prominent in individuals with darker skin tones, typically in a symmetric pattern on the face and neck. The pathogenesis is still unclear. Possible etiologic agents include UV radiation, hormonal changes related to pregnancy or thyroid abnormalities, as well as antiseizure and photosensitive medications. Increased melanocyte number and/or excess melanin production may be involved in the pathophysiology of this disorder. There are many therapies for melasma, including hypopigmenting agents, chemical peels, dermabrasion, and various types of lasers. Preventative modalities should also be considered in the management of this condition, such as minimization of UV exposure and avoidance of certain drugs when possible. Elucidation of the pathogenesis of this condition may lead to better, more specific treatments.

SEARCH METHODOLOGY

We performed a PubMed search for all articles relating to “melasma” and “chloasma” and found 75 articles of particular interest. We have also evaluated many other articles and book chapters as well. Pertinent evidence-based information relevant to the epidemiology, etiology, diagnosis, and therapeutic management of the disorder were selected and included in this chapter.

INTRODUCTION

The word melasma is derived from the Greek word “melas”, which means “black spot or color”. It is also commonly known as “chloasma”, and “the mask of pregnancy”, because of its tendency to occur during pregnancy. These hyperpigmented patches typically appear on the face and neck, but may occur in other locations as well, such as the upper limbs. The development of melasma is often associated with known etiologic factors, although some cases may be idiopathic. Melasma is primarily a cosmetic disorder. However, given its potential psychologic repercussions and impact on quality of life, it should be appropriately treated at the patient’s request.

EPIDEMIOLOGY

Approximately 5-6 million women are affected by melasma in the United States.¹ Ninety percent of melasma cases are seen in women, particularly in individuals with darker skin types.² Melasma is thought to be more prevalent among Latinos.³ Incidences as high as 80% have been reported in Hispanic women.⁴ It appears that there is a high incidence of melasma in individuals with skin type IV to VI, particularly those of South American, Mediterranean, Asian, and African American descent.⁵⁻⁸ Melasma may be more apparent in those individuals, but people of all races can be affected.¹ It occurs in approximately 50-70% of pregnant women, and sporadically in approximately 10% of men.^{3,9,10}

ETIOLOGY AND PATHOGENESIS

Many etiologic agents have been identified in melasma. However, in most cases occurring in men and in one-third of cases occurring in women, no known causes have been identified.⁵ UV radiation, female hormonal activity, endocrine organ dysfunction including ovarian, testicular and thyroid abnormalities, family history, cosmetic products, photo-sensitive and antiseizure medications make up the majority of the known associated risk factors.^{5,11,12} Although the pathogenesis remains unclear, the hyperpigmentation seen in this condition is caused by an increased amount of melanin in the skin. This occurs either via melanotic hyperpigmentation, in which there is increased stimulation of melanogenesis, or melanocytic hyperpigmentation, in which there is an increase in the number of melanocytes.⁵ The pigment’s distribution pattern, whether in the epidermis, dermis or both, plays a significant role in the clinical appearance of melasma.⁵ The most strongly associated risk factor is *UV radiation*.¹¹ In a study done in Puerto Rico, clinical onset and exacerbation were most prominent during the summer with increasing sun exposure, with significant improvement occurring during the winter.¹³ The etiologic role of UV radiation is also well supported by histologic evidence of solar elastosis.¹⁴ UV radiation appears to cause hyperpigmentation via two mechanisms: increasing the number of melanocytes, and increasing melanin production. UV radiation leads

to increased levels of dermal stem cell factor, the latter of which has been shown to cause *in vitro* melanocyte proliferation and may be over expressed in melasma.^{15,16} UV radiation is also known to stimulate excess melanin production. In particular, UVB causes a greater increase in melanin production in more darkly pigmented melanocytes, which offers a possible explanation for the greater prevalence of melasma in darker skinned patients.^{17,18} A possible mechanism is via UVB-induced stimulation of the alpha-melanocyte stimulating hormone (α -MSH) and adrenocorticotropic hormone (ACTH). Both are derived from propiomelanocortin (POMC) and induce cyclic AMP production, which in turn stimulates tyrosinase activity, thereby increasing melanin production.^{19–21}

Female *hormonal activity* is another significant risk factor. This idea is supported by the fact that melasma is much more common in women, and that it tends to occur during their reproductive years. The presence of melasma in up to 75% of pregnancies, the period of greatest hormonal expression, further supports a hormonal etiology.²² There is additional evidence in support of hormonal activity as an etiology for melasma. Upregulation of estrogen receptors in affected skin in melasma has recently been demonstrated.²³ Women taking oral contraceptive pills have a greater incidence of melasma.²⁴ Combined estrogen and progesterone hormone replacement therapy in post-menopausal women with osteoporosis is associated with melasma.^{25,26} Melasma has not been reported in women who are on estrogen-only regimens.⁸ There is an association between androgen replacement therapy and melasma in men.²⁷ Although the pathogenic mechanism of sex steroids in melasma remains unclear, studies have shown that both alpha and beta-estradiols stimulate tyrosinase activity as well as melanin extrusion in melanocytes.^{28,29} *Endocrine organ dysfunction* may play a role in melasma. There is an association between increased LH levels and decreased estrogen levels identified in nine nulliparous women with idiopathic melasma.³⁰ Similarly, another study in men with idiopathic melasma documented increased LH levels as well.³¹ One study showed a four-fold difference in the prevalence of melasma between patients with thyroid abnormalities and the control group.³² *Family history* is also a significant risk factor. Between 30–70% of patients with melasma report a positive family history.^{9,10,33} A study on one set of identical twins showed that both developed melasma, while other siblings living under similar conditions did not, lending further support for genetics as a risk factor for melasma.³⁴

DIAGNOSIS

Melasma should be distinguished from other disorders of hyperpigmentation. This is especially important for potentially disfiguring or malignant disorders such as melanoma. Table 14-1 offers a differential diagnosis. Melasma is a clinical diagnosis that may be supported with histologic

TABLE 14-1—Differential Diagnosis of Melasma

Postinflammatory hyperpigmentation (e.g., atopic dermatitis, drugs, acne)
Lentigo malignant melanoma
Epidermal nevi
Freckles
Café-au-lait macules
Solar lentigines
Tinea versicolor

evidence if necessary. On physical examination, melasma typically appears as one of three clinical patterns: centrofacial, malar and mandibular.³⁵ Rarely, it may appear on the upper extremities.^{8,25,26,36} The macules and patches are generally symmetrical in appearance, but may have irregular borders and a blotchy color distribution.^{37,38} There are three histologic patterns: epidermal, dermal, and mixed.¹³ The histologic type correlates well with the clinical appearance.^{13,18} Epidermal melasma appears light brown, while dermal melasma appears bluish grey because of the Tyndall effect. Enhanced color contrast is seen with Wood's lamp examination in areas of epidermal melasma, which may serve as a screening method for the three histologic types and may help guide treatment selection.

THERAPEUTIC MANAGEMENT

What Types of Preventative Modalities Are Available for Melasma?

An essential and effective preventative modality for melasma is protection from UV radiation. Broad-spectrum sunscreens with both UVA and UVB protection are recommended. Sun blocks may also be used. Examples include micronized zinc oxide and titanium oxide applications. The new general guidelines from the American Academy of Dermatology recommending the use of SPF 30 instead of SPF 15 should be followed and may provide some additional protection from this disorder, as well as others related to actinic damage. Patients may also consider other UV protective measures, such as wearing wide-brimmed hats during the day to protect the face from excessive sunlight. This is especially important since the face is the most commonly involved location for melasma. Logically, other preventative methods should focus on a reduction of exposure to other potential etiologic agents, such as oral contraceptive pills, cosmetics and phototoxic agents, with complete cessation of the offending agent where possible. However, this may not always be feasible, such as in the case of pregnancy. Therefore, a thorough discussion of personal costs versus benefits may be undertaken on a case-by-case basis between the physician and patient.

What Are the Current Treatment Modalities for Melasma?

Current treatment modalities for melasma can be broadly categorized into two groups based on their mechanism of action: those that disrupt the biochemical and physiologic pathways that lead to normal melanin expression in the skin, and those that physically disrupt the different layers of the skin. The first group consists of the topical hypopigmenting agents, which can be sub-classified based on their particular mechanism of action. Some inhibit the biochemical formation of melanin, such as hydroquinone, azelaic acid, kojic acid, and ascorbic acid, while others interfere with its physiologic distribution or expression in the skin, and include tretinoin, glycolic acid, liquiritin, and N-acetyl-4-s-cysteaminylphenol (NACP). Both achieve the same clinical effect of hypopigmentation. Physically disruptive agents induce local destruction of cells and rely on the skin's regenerative properties to achieve their clinical effects. They include chemical peels, lasers, dermabrasion, and photodynamic therapy. Figure 14-1 illustrates the site of action of the topical hypopigmenting agents as well as the physically disruptive modalities.

Hydroquinone is one of the most effective treatments for melasma, and is a tyrosinase inhibitor.³⁸ Application of a 4% solution of hydroquinone is considered the gold

standard, although 2-4% solutions are also used.³⁹ As the concentration increases, the effectiveness of the drug also increases, while the side effect profile simultaneously worsens. Exogenous ochronosis, contact dermatitis, and adjacent hypopigmentation are known side effects.^{40,41} 4-6 weeks of therapy may be necessary before a clinical response is seen.⁴ The use of hydroquinone is currently a topic of controversy in the United States, particularly since it has been banned in some parts of the world, such as the European and Japanese markets.^{42,43} The outcome of this debate remains to be seen, but has spurred interest in developing other effective hypopigmenting agents.⁴² Azelaic acid is also a tyrosinase inhibitor, originally isolated from *Pityrosporum ovale*.⁴⁴ 20% azelaic acid may be more effective than 2% hydroquinone.⁴⁵ Kojic acid is another fungal metabolites isolated from *Aspergillus oryzae* that also inhibits tyrosinase.⁴⁶ Ascorbic acid is thought to block melanin synthesis by inhibition of tyrosinase. 5% ascorbic acid has been found to be more tolerable than 4% hydroquinone, and although less effective, may potentially serve as an alternative treatment.⁴⁷

Tretinoin increases keratinocyte proliferation, thereby accelerating epidermal cell turnover and regeneration, and decreasing melanin accumulation.⁴⁸ It is known to be effective in lightening actinic macules.⁴⁹ Studies using a 0.1% solution of tretinoin have shown that significant clinical

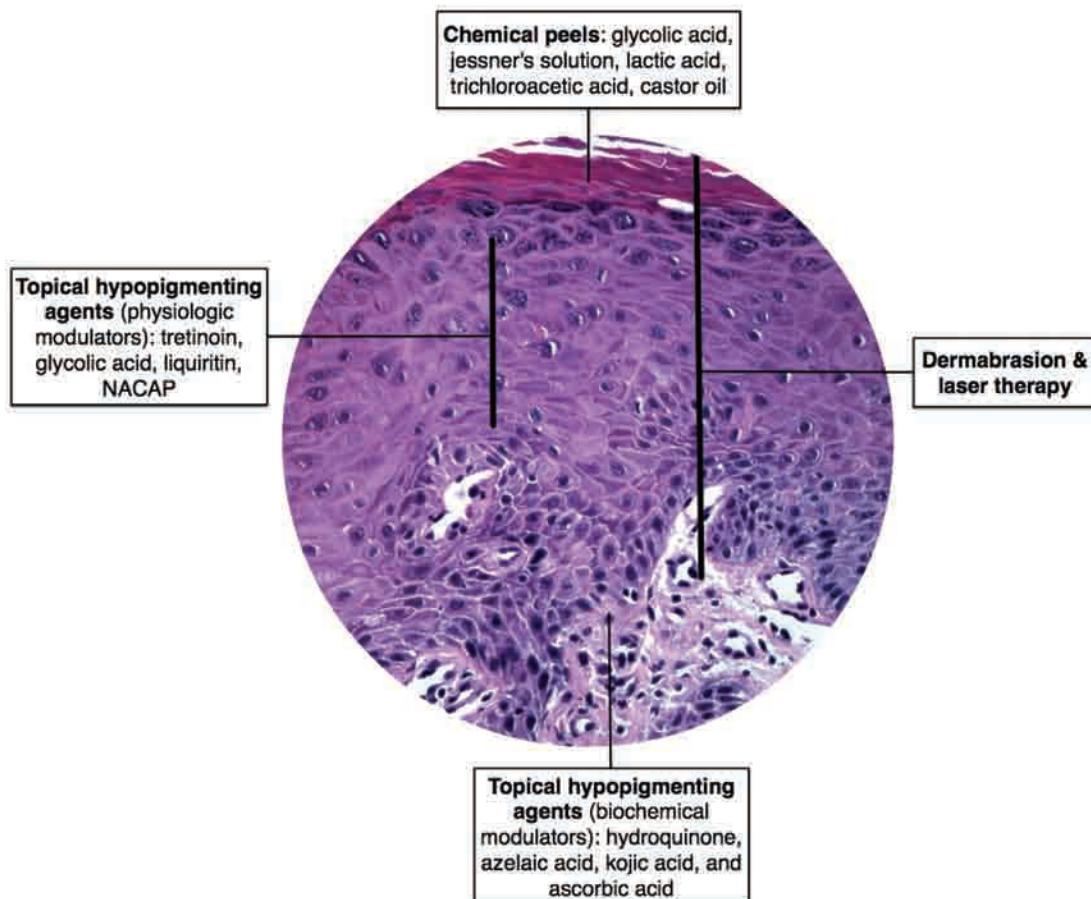


FIGURE 14-1 Site of action of therapeutic modalities for melasma.

improvements may take up to 24-40 weeks.^{50,51} Glycolic acid disperses melanin in the basal layer, increases dermal collagen synthesis, and stimulates epidermal cell lysis.⁵² Liquiritin, a liquorice extract, is also thought to dissipate melanin and can be used as a topical cream with minimal side effects.⁵³ N-acetyl-4-s-cysteamylphenol (NACP) decreases melanosomal transfer to keratinocytes, as well as the number of functioning melanocytes.

Physically disruptive agents tend to be useful in the treatment of recalcitrant melasma. *Chemical peels* induce skin exfoliation and subsequent revitalization. Glycolic acid peels are the most commonly used. A small study has shown that 1% tretinoin may be an effective and well-tolerated chemical peel.⁵⁴ Many other peeling agents are available, including Jessner's solution, salicylic acid, kojic acid, phenol-castor oil, lactic acid, and trichloroacetic acid.^{40,54,55} *Lasers* are primarily used for dermal melasma given its resistance to topical hypopigmenting agents. Q-switched lasers have been shown to effectively improve melasma.⁵⁶ Fractional laser therapy or photothermolysis causes microscopic zones of thermal damage in the epidermis and dermis, thereby reducing healing time when compared to other laser therapies. It is effective for resistant cases of melasma and can be safely used in dark-skinned patients.⁵⁷ A small pilot study reports 75-100% clinical resolution in 60% of patients.⁵⁸ *Superficial dermabrasion* physically disrupts the epidermis and dermis, and appears to have good long-term results. In one study, 97% of patients had no recurrence of melasma after 5 years post-treatment.⁵⁹ Side effects may include pruritus, milia, hypertrophic scars and permanent hypopigmentation.⁵⁹ Microdermabrasion may also offer some improvement.⁶⁰ Newer modalities for melasma include photodynamic therapy with aminolevulinic acid, and intralesional injection of tranexamic acid.^{61,62}

What's the Evidence for Combination Therapies?

Combination therapies do offer significant benefits when compared to monotherapy with a primary agent. In particular, many therapies have been tested as adjuncts to hydroquinone. For example, glycolic acid can hasten improvement and may be useful as an adjunct to topical hypopigmenting agents.^{63,64} Glycolic acid achieves this effect by thinning the stratum corneum and enhancing the penetration of other medications such as hydroquinone. One study showed significant improvement of melasma when 10% glycolic acid was added to 4% hydroquinone, vitamin C, E and sunscreens.⁶⁵ Kojic acid also appears useful when used in combination therapies. Clinical improvement increased from 45% to 60% when 2% kojic acid was added to a solution of 2% hydroquinone and 10% glycolic acid.⁴⁶ Sequential addition of corticosteroids after monotherapy with 20% azelaic acid showed earlier clinical improvement when compared to monotherapy with 20% azelaic acid.⁶⁶

Triple therapies, combining hydroquinone, tretinoin and a corticosteroid, are increasingly being employed, and are often considered first line therapy.^{35,40} Tri-Luma is a standard triple therapy containing 4% hydroquinone, 0.05% tretinoin, and 0.01% flutinolone. This triple combination has increased efficacy in facial melasma when compared to any combination of two components;⁶⁷ another study showed decreased severity of melasma in all skin types and races when this triple therapy was incorporated into a hydrophilic cream.⁶⁸ It is important to thoroughly discuss the risks and benefits of hydroquinone-based products with patients, given the current controversy surrounding these agents. A study on double therapy with tretinoin and mequinol showed equal effectiveness compared to 3% hydroquinone.⁶⁹ Two studies testing a combination Q-switched alexandrite laser (QSAL) and pulsed CO₂ laser produced better results than monotherapy with QSAL. The treatment options for melasma must be carefully selected for the appropriate clinical scenario. Figure 14-2 can serve as a summary of therapeutic options as well as a suggested management scheme.

What is the Prognosis for Melasma?

Given that melasma is primarily a cosmetic disorder with no significant systemic consequences, an evaluation of prognosis essentially revolves around the patient's self-perception of quality of life. We have identified two areas of importance to the clinical course or prognosis of melasma: the effect of the presence of risk factors such as oral contraceptives and pregnancy, and the impact of treatment choice.

The prognosis for melasma varies depending on the risk factors present in the patient. Similar to many other physiologic changes of pregnancy, melasma of pregnancy may undergo spontaneous remission within a few months after delivery.⁷⁰ However, melasma of pregnancy may persist postpartum in 9-30% of patients.^{22,71} One study suggests that melasma of pregnancy may recur in 7.6% of cases, even after postpartum remission from the first pregnancy. Melasma of pregnancy also presents a special challenge, given that many drugs have not been proven safe for use in pregnant women. Therefore, treatment is usually deferred in those patients. Melasma related to oral contraceptive use may resolve with cessation of the offending agent, although remission may be slow and incomplete.³⁷ Patient should thus be advised of this possibility prior to starting oral contraceptive therapy.

Prognosis also varies depending on the histologic type of melasma and whether or not the appropriate treatment is used. Epidermal melasma has a good prognosis when treated with topical hypopigmenting agents. This is good news, given that it appears to be the more common histologic subtype. One study found that this subtype was present in 69.2% of pregnant patients.⁷¹ Another study found epidermal melasma in 48.8% of cases.⁷² Dermal melasma, on the other hand, is very resistant

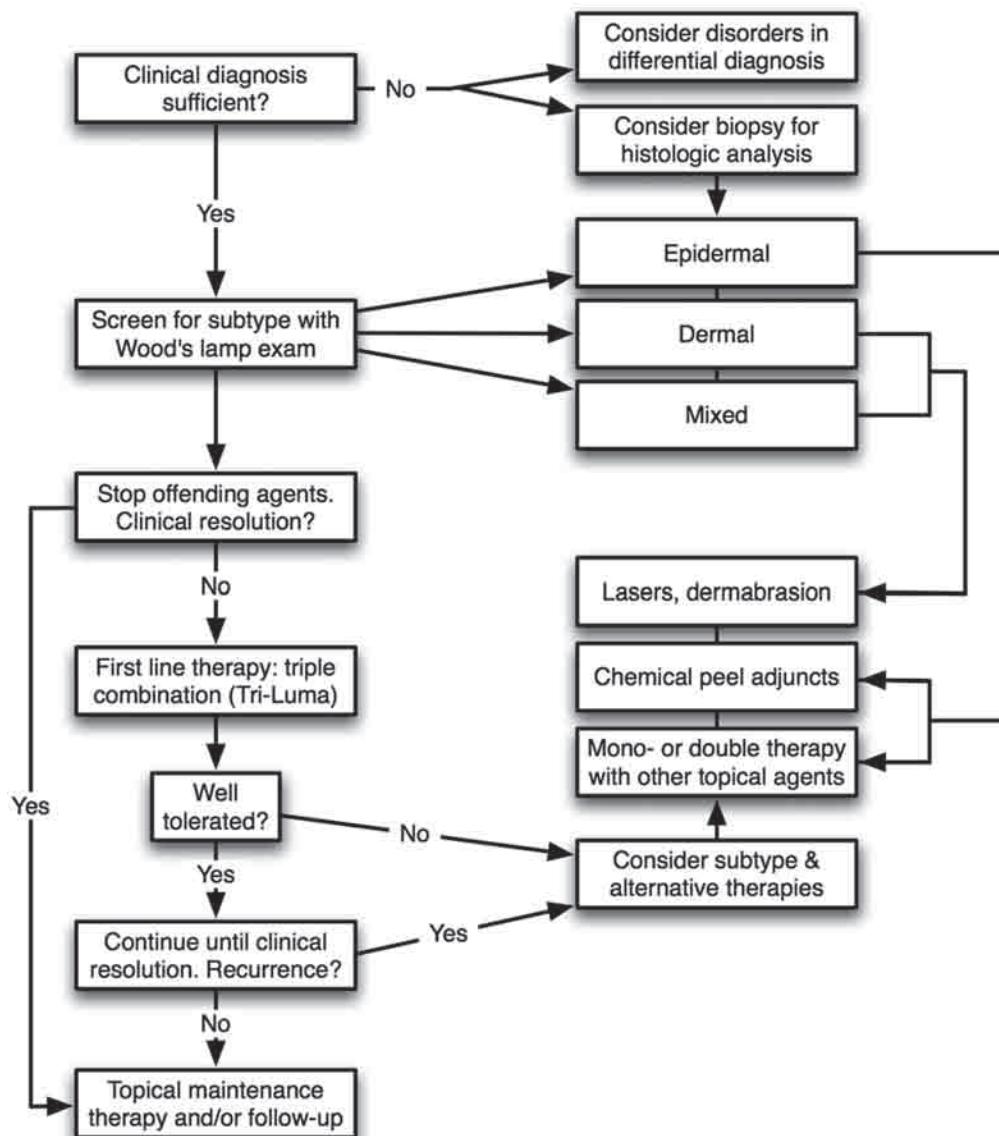


FIGURE 14-2 Suggested management scheme & therapeutic modalities.

to topical agents. Dermabrasion or lasers may be required for treatment of this type of melasma.³⁷ As expected, mixed type melasma requires a diversified approach to treatment, including both topical hypopigmenting agents and more invasive treatments such as lasers for clinical resolution.³⁸

What is the Impact of Melasma and its Effect on the Patient's Quality of Life?

Melasma can have a significant effect on the patient's quality of life, because of the psychologic impact of the disorder on self-perception. This has been demonstrated through the establishment of the Melasma Quality of Life Scale (MELASQOL) and its various adaptations.^{3,6,73} Studies have found minimal correlations between disease severity and quality of life. In other words, objective disease severity as assessed by a physician, using tools such as the melasma area and severity index (MASI), may not always coincide with the patient's perception of severity.^{6,74} This

may lead to under-diagnosis and possibly under-treatment of this disorder.⁴ The MELASQOL score focuses more on the psychologic impact of melasma. Disease severity strongly influences the aggressiveness of treatment choice, which in turn may affect the course and prognosis. Social life, recreation and leisure, and emotional well-being are reportedly the most affected areas of life in well educated White women, while physical health and money matters are also severely affected in Hispanic women.^{74,75} There is a consistent correlation between lower educational status and poor quality of life ratings for melasma.⁷⁵ In particular, facial blemishes appear to have a significant impact on quality of life of women.⁷³ 'What We Know' box on the following page provides a summary of the current evidence for melasma, a guide to what we know.

CONCLUSION

Melasma is a disorder of hyperpigmentation that primarily affects women in their reproductive years. It typically

What We Know

Epidemiology

- Melasma is primarily a facial disorder of women in their reproductive years.
- It may also be present in older women taking oral contraceptives or hormone replacement therapy, adolescents, and men, and may occur sporadically.

Etiology & Pathogenesis

- Risk factors include UV radiation, female hormonal activity, ovarian, testicular and thyroid abnormalities, family history, cosmetic products, photo-sensitive and antiseizure medications.
- The pathogenesis remains unclear.

Diagnosis

- Melasma is a clinical diagnosis, supported by histologic evidence if warranted.
- It appears as hyperpigmented macules in 3 clinical patterns: centrofacial, malar or mandibular.
- Melasma is classified into epidermal, dermal or mixed patterns of distribution of pigmentation.
- There are strong correlations between the histologic subtype and clinical appearance of the disease.

Therapeutic Management

- Broad-spectrum UV protection is an essential and effective preventative modality.
- Reduction of exposure to other risk factor may also be beneficial.
- Topical therapies are considered first line, whether they are use as mono, double or triple therapy.
- Topical therapies consist of various modulators of melanin synthesis and distribution.
- Biochemical modulators of melanin synthesis: hydroquinone, azelaic acid, kojic acid, ascorbic acid.
- Physiologic modulators of melanin distribution: glycolic acid, tretinoin, NACAP, liquiritin.
- Recalcitrant melasma cases show strong clinical improvement with physically disruptive agents.
- Physically disruptive agents: chemical peels, lasers, dermabrasion.
- Etiologic factors and treatment choice play an important role in the prognosis of the disorder.
- There is a potential disconnect between objective physician assessment of clinical severity and patient perception of severity, with a significant subsequent impact on quality of life.

N-acetyl-4-s-cysteamylphenol (NACAP).

appears as macules and patches on the face in either a central, malar or mandibular pattern. Several etiologic factors have been identified. Histologically, melasma can be classified as epidermal, dermal and mixed, depending on the primary location of melanin accumulation. The histologic classification may influence treatment selection. Epidermal melasma tends to respond well to topical hypopigmenting agents. Dermal melasma tends to be more resistant to topical hypopigmenting agents. Mixed melasma requires a more varied approach. More invasive treatments such as chemical peeling, various lasers, and dermabrasion may be necessary in cases of recalcitrant melasma. Triple combination therapies with topical agents are considered first line treatments. If poorly tolerated, the patient may be switched to single or double therapy. Recalcitrant melasma can be treated with chemical peels in combination with topical agents, or with lasers and dermabrasion. Topical agents may be used as maintenance therapy. There may be a significant disconnect between the physician's objective assessment and the patient's subjective experience of disease severity. Although the disorder is primarily cosmetic in nature, adequate treatment is warranted at the patient's request.

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Treatment of Psoriasis

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INTRODUCTION

Psoriasis vulgaris is a chronic inflammatory disease which affects multiple organ systems, presenting predominantly with skin and joint manifestations. It is characterized by erythematous, scaly plaques and papules. Such lesions can be painful and pruritic and can significantly impact a patient's quality of life (QOL). Psoriasis affects approximately 2% of the population, and is associated with psoriatic arthritis (a seronegative spondyloarthropathy), inflammatory bowel disease, cardiovascular disease and diabetes.

Plaque psoriasis is the most common form of psoriasis, with characteristically well-demarcated, erythematous scaly plaques present on the skin. While favored sites include the buttocks, lower back, scalp, and extensor surfaces including the elbows and knees, any area of the skin may be affected. When plaques are present on the soles or palms, painful cracking and fissuring may occur. Approximately 80% of patients have mild to moderate psoriasis and the remaining 20% have moderate to severe psoriasis, in which greater than 5% of the BSA is affected or specific areas including face, genitals, hands or feet are affected.¹

Inverse psoriasis classically presents in areas of skin folds including the axilla, groin, inframammary, perineal and intergluteal locations. Erythrodermic psoriasis is characterized by generalized full-body erythema with varying degrees of scaling, and symptoms including hypothermia, chills, and fluid loss secondary to the highly inflammatory skin lesions. Pustular psoriasis can be either localized or generalized and represents clinically visible collections of neutrophils. The acute, generalized form of pustular psoriasis may present with fever. Guttate psoriasis is characterized by small, drop-like pink papules on the trunk and extremities. Guttate psoriasis may be precipitated by a preceding upper respiratory infection caused by group A beta-hemolytic streptococcus and is often seen in younger patients.

PSYCHOSOCIAL ISSUES AND PATIENT RESOURCES

As the skin manifestations of psoriasis can vary widely in distribution, severity and the percentage of body surface area (BSA) affected, treatment must be individualized.

There is an array of possible therapies to choose from depending on the character of the skin lesions, QOL considerations and patients' concomitant medical issues. However, the first step in the treatment of psoriasis includes addressing psychosocial issues and patient education. The National Psoriasis Foundation is a tremendous resource in the United States which provides information to patients about psoriasis, treatment options, advocacy programs and support groups. On the National Psoriasis Foundation website (www.psoriasis.org), patients can find informative brochures about psoriasis, psoriatic arthritis, medications used to treat the disease, illustrated storybooks for children, and information about advocacy programs such as the Walk to Cure Psoriasis. Another available resource is Psoriasis Cure Now (www.psoriasis-cure-now.org) which specifically targets lawmakers in advocating for research and where patients can access information about current available therapies.

The psychosocial impact of psoriasis can be profound, and it is integral for clinicians to recognize that this psychologic impact may not necessarily relate to the clinical extent or severity of a patient's disease. Psoriasis has been associated with a lack of self-esteem and a higher incidence of depression, the prevalence of which may be as high as 60%.^{2,3} In some patients, the depression is so severe that patients may contemplate suicide. In one particular study, 5% of patients with psoriasis reported active suicidal ideation and 10% of patients reported a wish to be dead.⁴

Psoriasis can affect a patient's occupational functioning and personal relationships. In one study examining 300 patients with psoriasis, the disability experienced by patients with psoriasis was found to be comparable to patients with cancer, heart disease, diabetes, and depression.⁵ The Dermatology Life Quality Index is widely used to measure QOL in psoriasis studies.⁶ Another QOL tool, the Psoriasis QOL 12-item instrument, can help discriminate among various degrees of psoriasis severity and can be responsive to clinical change due to treatment.^{7,8} Another instrument which incorporates QOL measurement with a measurement of psoriasis severity by BSA is the Koo-Menter Psoriasis Instrument, which can help clinicians evaluate a patient's physical psoriasis severity as well as impact on QOL.⁹ The impact of the disease on

patients must be considered when evaluating and balancing the potential risks and benefits of treatment. The psychosocial impact can be large even when patients have a small BSA affected by psoriasis, for instance, patients with palm and sole involvement are often impacted more than patients with more severe involvement on other parts of the body.^{10,11}

PATIENT ADHERENCE TO TREATMENT

Adherence is defined as the degree to which a patient uses treatment as prescribed by their healthcare provider.¹² Multiple factors play a role in adherence to treatment, including the treatment provided, the clinical severity of psoriasis, and the patient themselves. Some 40% of patients report not using their treatments as directed because of inconvenience, time constraints, cost, complicated instructions and perception of low efficacy^{13,14}; actual nonadherence rates may be much higher. A Danish study found that 50% of psoriasis treatment prescriptions weren't even filled.¹⁵ Treatment outcome may affect a patient's satisfaction with treatment, which in turn may affect adherence to treatment. Poor adherence to treatment should be considered when a patient's disease is not improving as expected.¹⁶ Encouraging adherence is a critical consideration when treating chronic diseases such as psoriasis.

Measures to improve patient adherence include establishing a strong physician-patient relationship, addressing the psychosocial impact of psoriasis, motivating patients to use their medication by having them return for an appointment shortly after beginning treatment, using a treatment vehicle which the patient prefers, and making the treatment plan simple for the patient to both understand and follow.¹⁷ Considering patients' preference for different vehicles may help improve adherence. Although ointment formulations were traditionally considered to be more potent than cream formulations (particularly for dry, scaly conditions), clinicians must assess and consider whether the patient will adhere to such treatment or if other vehicles such as creams, solutions, foams or sprays would be more suitable for a particular patient. Patients should be involved in the decision-making process regarding what particular therapy and vehicle they will be prescribed. Inevitably, the best treatment for a patient is the one, which they will actually use consistently. Finally, reducing the time between initiation of treatment and the first return visit (or other form of contact) may motivate a patient to improve initial adherence and treatment outcome.¹⁷

EVALUATION OF TREATMENT

Evaluation of psoriasis treatment in clinical trials incorporates specific assessment tools. The Psoriasis Area and Severity Index (PASI) is a commonly used measure of psoriasis severity for patients with moderate-to-severe disease, assessing erythema, induration, scaling, and the

percentage of affected BSA.¹⁸ The PASI is not frequently used in routine clinical practice. In clinical trials, a 75% improvement in the PASI (PASI75) is used as a measure of psoriasis treatment success. This is a stringent measure of success, as many patients with less than 75% improvement in PASI may be very pleased with their degree of improvement.

Other psoriasis severity measures include the Physicians Global Assessment (PGA) whereby clinical investigators estimate the overall severity of a patient's psoriasis on a scale from clear to severe.¹⁸ Clear or almost clear status is typically used as the primary outcome measure for assessing success in trials for mild-to-moderate psoriasis. Another quantitative assessment of psoriasis severity includes BSA measurement, approximating 1% of BSA to the area of a patient's open handprint, extending from the wrist to fingertips.¹⁸ In clinical practice, dermatologists use subjective assessments of psoriasis severity, taking into consideration location, induration of plaques, symptoms, BSA involvement, and the physical and emotional disease burden carried by the patient.

TOPICAL TREATMENTS FOR PSORIASIS

The majority of psoriasis patients have limited disease comprising less than 5% BSA, and topical treatment may be suitable for them. Many topical agents provide reasonably high efficacy and safety. Furthermore, topical treatments may be used as adjunctive therapy to systemic treatment, biologic agents, and phototherapy. Recommending the use of topical treatments as monotherapy when the psoriasis is too extensive for the patient to apply topical treatment to all the spots is probably not a rational treatment strategy.¹⁹

Topical vehicles include ointments, creams, gels, foams, solutions, sprays, oils, lotions, tape, and shampoo. Depending on the body site and patient preference, a particular vehicle can be chosen. For instance, some patients will prefer to use a medicated shampoo for the treatment of scalp psoriasis, while others may prefer a solution or foam. Topical agents can be used in combination, but there may be compatibility issues. For example, acid products should not be used with calcipotriene, as calcipotriene is not stable in an acid environment.¹⁹ Topical agents may be used continuously or intermittently, depending on the nature of the patient's disease and the topical agent being used. Generally, more potent agents are used intermittently to decrease the potential risk of side effects.

Topical Corticosteroids

Topical corticosteroids are available in a variety of strengths and formulations, and remain a widely utilized topical treatment of psoriasis. Mechanisms of action of corticosteroids include decreasing inflammation, decreasing proliferation, and vasoconstrictive and immunosuppressive effects. Topical steroids range in strength from

class I (superpotent) and class II (potent) to class VII (least potent).

The short term use of class I (superpotent) topical steroids for psoriasis has been established in vehicle-controlled studies. In a 2-week double-blind controlled trial (n=204), patients with moderate to severe psoriasis treated with halobetasol propionate ointment had a 92% improvement in PGA as compared to the vehicle group, which experienced a 39% improvement.²⁰ In another double-blind study of patients treated with clobetasol solution for moderate to severe psoriasis, 81% of patients achieved 50% or more clearance after 2 weeks of use, compared to 22% in the vehicle group.²¹ One of the newer formulations for topical steroids is a foam vehicle. In one 2-week double-blind trial (n=81) of patients with mild to moderate psoriasis treated with clobetasol foam, 58% of patients achieved moderate or better improvement, and in a similar trial (n=279) 68% of patients achieved clearance or near clearance of psoriasis while using clobetasol foam.^{22,23}

In a double-blind study of patients with psoriasis (n=35) treated with desoximetasone cream (class II) for 3 weeks, 68% of treated patients compared to 23% in the vehicle-treated group achieved overall improvement.²⁴ In a double-blind study of patients with scalp psoriasis (n=27) 74% of patients treated with halcinonide solution (class II) achieved good or excellent response compared to 45% of patients in the vehicle group.²⁵ In two randomized studies of patients with moderate to severe psoriasis (n=383), 68 to 69% of patients treated with a class III agent, fluticasone propionate, had excellent, good or clear skin after 4 weeks of usage, compared to 29% in the vehicle group.²⁶ In a double-blind placebo-controlled trial for patients with moderate to severe scalp psoriasis (n=172), 72% of patients treated with betamethasone valerate foam (class IV) achieved an improvement in the PGA score compared to 47% in the placebo group.²⁷ In another study among 40 patients with psoriasis, 70% of patients treated with betamethasone valerate foam for 3 months achieved greater than 50% improvement compared to 24% in the placebo group.²⁸ In a double-blind vehicle-controlled study of patients with mild to moderate psoriasis (n=190), 41% of patients treated with hydrocortisone 17-butyrate 21-propionate cream, a class V agent, responded with good or excellent improvement, compared to 18% in the vehicle group.²⁹ In a randomized, double-blind trial of patients with scalp psoriasis (n=89), 83% of patients treated with a class VI agent, fluocinolone acetonide 0.01% oil, had good or better improvement from baseline, compared to 36% of patients treated with a vehicle oil.³⁰ In one large systematic review of topical corticosteroid treatment for psoriasis, potent and superpotent strength formulations were more efficacious compared to mild and moderate topical steroids.³¹

The primary limitation of the aforementioned studies involving topical corticosteroids is the short time duration during which safety and efficacy were evaluated. Notably,

psoriasis may recur following discontinuation of the topical corticosteroid. Psoriasis may also become resistant to topical corticosteroids over time, a phenomenon termed tachyphylaxis. While traditionally tachyphylaxis was presumed to result in some type of desensitization to the drug, it may be largely because of poor adherence.

The recommended dosing of topical corticosteroids for the indication of plaque psoriasis is 1-2 times daily as monotherapy, and can be adjunctive to phototherapy and systemic agents (though there is some concern that use of topical corticosteroids with phototherapy may reduce the duration of remissions associated with phototherapy). For class I steroids, the available data support a duration of 2-4 weeks of treatment, and for less potent corticosteroids there is no specific endpoint recommended. For superpotent topical steroids such as clobetasol and halobetasol, the weekly use should not exceed a maximum of 50g.¹⁹ However, following a therapeutic clinical response, a gradual reduction in patient usage is recommended. Lower potency corticosteroids can be used in the intertriginous areas, face, and on infants.¹⁹ Clinicians should consider that highly potent topical steroids have a greater efficacy than less potent treatment agents. When prescribing a topical corticosteroid, the vehicle, the area of usage, patient preference, and age of the patient should all be considered.

Adverse effects of topical corticosteroids can be either local or systemic. Local toxicities include local skin atrophy, development of striae, contact dermatitis, rosacea and telangiectasias. Potential systemic effects include hypothalamic-pituitary-adrenal (HPA) axis suppression, which can occur with continued use of medium or high-potency topical steroids. Increased intraocular pressure, cataracts, glaucoma, and avascular necrosis of the femoral head are rare adverse effects. Limiting the use of topical corticosteroids to intermittent use can help decrease the risk of such toxicities. There is no specific baseline monitoring recommended, but intermittent monitoring for cutaneous atrophy is advised if patients are using the medicine continuously. Children using topical corticosteroids extensively over the long-term should have their growth assessed on a regular basis. For infants and children, there is a higher risk of systemic side effects because of an increased skin surface/body mass ratio. Topical corticosteroids are pregnancy category C.

Vitamin D Analogues

Calcitriol is a natural vitamin D molecule, and calcipotriol (calcipotriene) is a synthetic vitamin D analogue used for the treatment of psoriasis. The mechanism of action is believed to be mediated by binding to vitamin D receptors, leading to keratinocyte differentiation and inhibition of proliferation. Calcitriol is available as an ointment and calcipotriene is available in a solution and cream form in the United States. In a randomized study of patients with scalp psoriasis, 60% of patients had clearance or marked

improvement after treatment with calcipotriene solution compared to 17% in the vehicle group.³² In one randomized placebo-controlled trial of patients with plaque psoriasis, 70% of patients had a PASI 75 improvement when treated with calcipotriene ointment as compared to 19% in the placebo group.³³ In a right-left comparison study, 74% of patients treated with calcipotriol had improvement or clearance compared to 18% in the vehicle group.³⁴ In a 52-week trial evaluating calcitriol, 324 patients with mild to moderate plaque psoriasis were treated with calcitriol ointment 3 microg/g twice daily. Improvements in a global severity score were seen over the course of treatment and the ointment was considered to be safe and well-tolerated throughout 52 weeks of treatment with no effect on calcium homeostasis.³⁵ Calcitriol is thought to be better tolerated for use on sensitive areas such as the face, flexural surfaces, and the hairline, causing less irritation.³⁴

Vitamin D analogues are recommended for twice-daily dosing to affected areas. Adverse reactions can include irritation in lesional or perilesional skin, a reversible elevation of serum calcium if large quantities are used (>100 g/week of calcipotriol or >200 g/week of calcitriol), and photosensitivity. There is no contraindication to combining these agents with ultraviolet B (UVB) phototherapy, but calcipotriene can be inactivated by ultraviolet A (UVA) light and should only be applied after and not before exposure to UVA light.³⁶ These agents are pregnancy category C, but there is no information on excretion into breast milk. Use among pediatric patients appears to be safe.³⁷

A calcipotriene/betamethasone propionate ointment preparation was studied in 1603 patients for 4 weeks. 48% of patients in the treatment group achieved absent to mild disease compared to 16.5% of patients in the calcipotriene group.³⁸ In a 52-week long study (n=828), at least 69% of patients treated with calcipotriene 0.005% and betamethasone 0.064% achieved almost clear or clear status, and there were no drug-related serious adverse events including HPA axis suppression after 52 weeks of usage.³⁹

Tazarotene

Tazarotene is a topical retinoid approved for the treatment of psoriasis. It is thought to normalize keratinocyte differentiation and diminish hyperproliferation. In one vehicle-controlled trial, there was 50% or more improvement seen in 63% of patients treated with tazarotene 0.1%, compared to 31% of patients treated with vehicle gel for 3 months.⁴⁰ In two large controlled trials (n=1303), 40%-51% of patients treated with tazarotene 0.1% and tazarotene 0.05% cream, achieved an overall lesion assessment of none, mild, or minimal after 12 weeks of treatment.⁴¹

Topical tazarotene is indicated for once daily use. Most common side effects include local skin irritation and photosensitivity, and the irritation can be minimized by combination use with topical corticosteroids.¹⁹ One controlled study of tazarotene with UVB light showed that combined

use decreased the amount of ultraviolet light needed to for a good clinical response.⁴² Tazarotene is pregnancy category X as it is a teratogenic retinoid, and cannot be used during pregnancy. Excretion in human milk is unclear. For pediatric usage, tazarotene is approved for acne ages 12 years and older, but there is no data for pediatric psoriasis patients.

Tacrolimus and Pimecrolimus

Tacrolimus and pimecrolimus are topical calcineurin inhibitors, which help block the synthesis of inflammatory cytokines, which play a role in psoriasis. These agents are efficacious when used under occlusion for the treatment of plaque psoriasis. Tacrolimus and pimecrolimus are also effective for facial and intertriginous psoriasis without occlusion, avoiding concerns about atrophy and other side effects associated with topical corticosteroids in these sensitive areas. In a randomized, controlled study of patients with facial and intertriginous psoriasis (n=167), 65% of patients had a clear or almost clear response after 8 weeks of treatment with tacrolimus 0.1% ointment, compared to 31% in the placebo group.⁴³ In another randomized, double-blind study of patients with intertriginous psoriasis (n=57), 71% of patients had clear or almost clear response after 8 weeks of treatment with pimecrolimus 0.1% cream, compared to 21% in the placebo group.⁴⁴

Tacrolimus and pimecrolimus are not FDA-approved for psoriasis but may be especially helpful off-label for psoriasis affecting the face and intertriginous areas. These topical agents can be applied twice daily with no set endpoint. Common adverse effects include a burning sensation, irritation, and itching. There is a controversial 'black box' warning which has been issued in the United States by the FDA for both tacrolimus ointment and pimecrolimus cream, because of a lack of long-term safety data and a potential risk for development of lymphoma.^{45,46} Notably, there is currently no clinical evidence suggesting an association between these topical agents and an increased risk of malignancy, including lymphoma.⁴⁷ These topical calcineurin inhibitors are pregnancy category C and are not recommended for use in nursing mothers. These agents are approved for adults and children at least 2 years of age with atopic dermatitis.

Coal Tar

Coal tar is composed of thousands of compounds, distilled from coal, and has been used in the treatment of psoriasis for nearly a century. Coal tar is thought to suppress DNA synthesis in keratinocytes, but its mechanism has not been fully elucidated. Combination of crude coal tar with ultraviolet light has been used in the intensive Goeckerman treatment regimen since the 1920s, and is effective for moderate to severe psoriasis. In a double-blind randomized study of patients with mild to moderate psoriasis (n=324), patients treated with 1% coal tar lotion had better

improvement in PASI compared to those treated with a 5% coal tar extract.⁴⁸ In another study (n=18), patients treated with 5% liquor carbonis detergens (LCD) had a greater improvement compared to treatment with emollient.⁴⁹

Coal tar is available in numerous formulations. Coal tar is often poorly tolerated by patients because of cosmetic issues such as staining of clothes and odor of tar. This may limit patients' adherence to treatment. Adverse events can include photosensitivity, irritant contact dermatitis, and folliculitis. In humans, there is no convincing data to suggest an association between coal tar and increased risk of carcinogenicity, and epidemiologic studies do not show an increased risk of skin cancer in patients using coal tar.⁵⁰ However, one study did demonstrate increased carcinogen excretion, specifically urinary 1-hydroxypyrene, from urine of patients treated with topical coal tar.⁵¹ In a recent literature review, authors concluded that topical coal tar can be used for short time periods during pregnancy.⁵² Coal tar compounds should be used with caution in pediatric patients.

Anthralin

Anthralin has been used topically for the treatment of psoriasis but is used less frequently as more cosmetically acceptable agents are currently available. Anthralin may help normalize keratinocyte differentiation and prevent T-cell activation.⁵³ In one small controlled study, patients using upto 2% concentration of anthralin twice daily for 4 weeks had better results compared to placebo.⁵⁴ In another controlled study, patients receiving 1 minute of treatment with 2% dithranol daily for 3 weeks had better results compared to placebo.⁵⁵

Anthralin is most commonly used for short contact therapy in an outpatient setting. There are several doses available, but treatment can begin with a 1% concentration and increasing concentration over time as tolerated. Common side effects include irritation of the skin, as well as staining of skin and clothing. There is no reported long-term systemic toxicity associated with anthralin. Anthralin should be applied cautiously, and patients who are exposed to anthralin for more than 2 hours may experience increased frequency of irritation. This agent should be applied cautiously to intertriginous zones and the face because of the potential for skin irritation. Anthralin is pregnancy category C and should be used with caution in pediatric patients.

Salicylic Acid

Salicylic acid is a topical keratolytic agent.⁵⁶ There have been no placebo-controlled studies evaluating salicylic acid monotherapy for psoriasis, but salicylic acid has been combined with other topical treatment agents, whereby it may help increase skin penetration of other agents secondary to its keratolytic effect. In a comparator study

of tacrolimus and salicylic acid versus tacrolimus alone (n=24), there was greater efficacy in the combination group.⁵⁷ In another study of patients with moderate to severe psoriasis (n=408), salicylic acid and mometasone was more effective than mometasone alone.⁵⁸ Salicylic acid should not be combined with other salicylate drugs. Sufficient systemic absorption to cause salicylism can occur if applied to a large percentage of BSA or in patients with liver or renal dysfunction. Salicylic acid blocks UVB, and application immediately prior to UVB phototherapy is not recommended. Salicylic acid usage appears to be safe in pregnancy but should be avoided in children because of the risk for systemic absorption.

PHOTOTHERAPY AND PHOTOCHEMOTHERAPY

Ultraviolet (UV) phototherapy includes narrowband UVB phototherapy (NB-UVB), broadband UVB phototherapy (BB-UVB), psoralen with UVA (PUVA) and excimer laser treatment. The effects of UV therapies can include rapid depletion of dermal and epidermal lymphocytes, dendritic cells, and macrophages.⁵⁹

Phototherapy is frequently utilized for patients whose psoriasis may be moderate to severe, and cannot be controlled with topical medications. UVB phototherapy is a first-line treatment option in moderate-to-severe psoriasis patients because of its efficacy, cost effectiveness, and safety profile. Furthermore, phototherapy may be considered as a suitable treatment option for patients with concomitant medical problems for whom systemic and biologic agents are not options. Patients must be able to receive phototherapy treatments regularly, often 3 times per week initially. This requirement can be burdensome for some patients, and efficacy will be limited if patients are not able to adhere to their treatment schedule.

Broadband-UVB and Narrowband-UVB Phototherapy

Ultraviolet B light has been utilized for the treatment of psoriasis since the 1920s, beginning with the Goeckerman treatment regimen in 1925. However, UVB in the form of sunlight has been used much longer than this. UVB light may lead to decreased proliferation of keratinocytes and decreased numbers of Langerhans cells, affecting antigen presentation.⁶⁰ Broadband UVB light ranges from 280-320 nm, and early studies established its efficacy in the treatment of psoriasis. In one study, 20 of 28 patients treated with erythemogenic doses of BB-UVB phototherapy experienced resolution of plaque psoriasis.⁶¹ In another trial, 90% of psoriatic patients experienced complete disease clearance with BB-UVB combined with petrolatum 3 times weekly for 3-13 weeks.⁶² Remission times have also been prolonged when using BB-UVB for maintenance therapy.⁶³

Narrowband-UVB light uses only a limited range of the UVB spectrum, emitting a distinct band of high-intensity light from 311 to 313 nm. Based on earlier studies, the 313-nm wavelength is thought to have the greatest risk/benefit ratio for psoriasis.^{64,65} Although NB-UVB was initially used more frequently in Europe, it is now utilized worldwide for the treatment of psoriasis.

One pilot study (n=10) comparing the efficacy of NB-UVB to BB-UVB in patients with psoriasis, found that NB-UVB is more efficacious.⁶⁶ In one right-left study comparing NB- and BB-UVB, 60% of patients had similar efficacy regardless of which UVB treatment was used, while the remaining 40% of patients had better results when treated with NB-UVB.⁶⁷ In another right-left study, there was faster clearing among patients treated with NB-UVB, compared to BB-UVB phototherapy.⁶⁸ Additionally, in another study, there was histopathologic resolution of 59% of psoriatic lesions treated with BB-UVB phototherapy, compared to 88% of psoriatic lesions treated with NB-UVB phototherapy.⁶⁹ Maintenance therapy with NB-UVB may also be beneficial. In one randomized controlled trial, 55% of patients who received maintenance therapy with NB-UVB twice weekly for 4 weeks, then weekly for 4 weeks, after 3 months of initial treatment were in remission at 1 year.⁶¹

The long-term safety data of UVB therapy remains controversial. It has not been established whether UVB phototherapy is carcinogenic in humans but overall results suggest that UVB therapy is a safe treatment modality. In a comprehensive review of BB-UVB and skin cancer risk, 11 clinical studies of 3400 participants were examined.⁷⁰ No published study showed an increased skin cancer risk, with the exception of one PUVA cohort study demonstrating an increased rate of genital tumors in men who had received PUVA phototherapy and BB-UVB. The contemporary standard of care thus includes genital shielding. There was no increased skin cancer risk in a retrospective 25-year study of 280 patients treated with BB-UVB and coal tar.⁵⁰ Furthermore, a retrospective study of patients with psoriasis receiving UVB phototherapy from 1994 through 2000 did not show an increased risk of skin cancer associated with either NB- or BB-UVB phototherapy.⁷¹

Treatment recommendations for UVB light, as indicated for generalized psoriasis, vary and specific treatment protocols vary widely. Initial dosing for BB-UVB therapy can be according to skin type, ranging anywhere from 20-60 mJ/cm² with subsequent incremental increases of 5-20 mJ/cm². For NB-UVB, the initial dosage according to skin type may range from 300-800 mJ/cm² and incremental dosage increase ranging from 100-150 mJ/cm².⁷² Dosage can also be calculated according to minimal erythema dose (MED), beginning with an initial NB-UVB dosage of 50% MED with subsequent increases at 10% the initial MED.⁷² Treatments may range from 2-4 times per week initially, with a course ranging from 15-25 treatments depending on the patient's clinical response. For NB-UVB, a single

course may range from 15-20 treatments but is generally longer for BB-UVB, with 20-30 treatments usually needed to induce clearance.

Adverse events can include erythema, burning, irritation and pruritus along with a theoretical risk of carcinogenesis. Patients must notify the phototherapy staff of new medications, as caution should be exercised when using photosensitizing medications. Furthermore, when UVB light is used in conjunction with retinoid agents such as acitretin, the dosage of UVB light may need to be reduced. UVB phototherapy is generally considered to be safe during pregnancy and in pediatric patients, although there have been no formal studies conducted in children.

PUVA Phototherapy

PUVA treatment refers to combining UVA light, at a wavelength of 320-400nm, with the use of 5- or 8-methoxysoralen which helps to sensitize cells to light. Psoralens intercalate between DNA bases, and form cross-links which can prevent replication of DNA following exposure to UVA light. Additionally, PUVA may lead to death of antigen presenting cells.⁷³ Psoralens can be administered topically, through soaking in a dilute solution or by painting a higher concentration topical psoralen agent directly on the lesions. Psoralen can also be administered orally, but some patients do not tolerate oral psoralen because of gastrointestinal complaints such as nausea. In the United States, the only available oral psoralen is 8-methoxysoralen but in Europe 5-methoxysoralen is used as well.

In one large multicenter study (n=1308), evaluating PUVA in the treatment of psoriasis in the United States, Fitzpatrick skin type was used to determine the initial dose, and incremental increases in the dosage of light were fixed.⁷⁴ Patients were treated 2-3 times weekly followed by high intensity, long-wave UVA light. In this study, 89% of patients achieved clearance of their psoriasis, and once remission was induced, there was no difference in a maintenance regimen of once weekly, once every other week, or once every third week. In another large, multicenter trial (n=3175) conducted in Europe, the minimal photo-toxic dose was used to initiate therapy and incremental increases in dosage were based upon skin response.⁷⁵ Patients received an average of twenty exposures to UVA light required for clearance over 5.3 weeks, and 89% of patients overall achieved clearance. Comparing these two studies, the European study utilized approximately half the total cumulative UVA dose for clearance of psoriasis as compared to the United States study. In two systematic reviews examining PUVA studies, between 70-100% of patients treated with PUVA achieved clearance of psoriasis, generally within 24 treatment sessions.^{76,77} Although many patients experience remission for up to 6 months following PUVA treatment, some patients require maintenance PUVA 1-2 per month to maintain good control of the disease.

Bath PUVA therapy can be as efficacious as oral PUVA, but this form of therapy is not used frequently in the United States.⁷⁸ Soak PUVA may be an effective therapy for psoriasis affecting the palms and soles, whereby 8-methoxypsoralen is dissolved in water. UVA light should generally be administered 30 minutes after a topical psoralen is applied, whether through soak or paint.

PUVA is known to lead to skin aging, multiple lentigines, and an increased risk of nonmelanoma skin cancers.⁷⁹ This risk may correlate with a total cumulative dosage of UVA light, and increases in individuals who have undergone more than 200 PUVA treatments.⁸⁰ One large-scale prospective study in the United States identified an additional risk of melanoma with increasing UVA exposure after 15 years of follow-up, primarily in patients who had received at least 250 PUVA treatments.⁷⁹ Another large-scale, long-term Scandinavian study with the same length of follow-up did not show an increased risk of melanoma.⁸¹ The basis for this difference is not clear, but limiting lifetime exposure to 200 PUVA sessions may help minimize the risk of skin cancer in at-risk patients and in patients with lower Fitzpatrick skin types.⁸² Furthermore, patients with a history of PUVA treatment may not be appropriate for treatment with immunosuppressive agents such as cyclosporine because of the potential for skin cancers to occur.

General recommendations for PUVA include oral administration of 8-methoxypsoralen at 0.4-0.6 mg/kg prior to exposure to UVA. Treatment can be administered 2-3 times weekly initially. An initial course of PUVA may be under 25 treatments, depending on clinical response. Patients should wear ultraviolet-protective eyewear for at least 12 hours following ingestion of psoralen. Patients must continue to undergo full body skin checks by dermatologists. PUVA is considered pregnancy category C and there have been no studies commenting on the use of PUVA in pediatric patients.

Targeted-UVB Phototherapy

Targeted UVB phototherapy has become available through the 308-nm excimer laser and a variety of nonlaser devices. These localized treatment devices can target psoriatic plaques without affecting perilesional or unaffected areas of skin. In a pilot study evaluating the 308-nm excimer laser for the treatment of psoriasis, 8-16 times the MED was used and 11 of 16 patients achieved a PASI 75 after 4 weeks.⁸³ In another study, there was greater than 95% clearance of psoriatic plaques following an average of just 10.6 treatments, when using dosages at 1-3 MED, which was considered medium-dose therapy.⁸⁴ A multicenter study was conducted (n=124) in which patients with plaque psoriasis were treated initially with a dosage of 3 MED; after an average of 6 treatments, 72% of patients achieved clearance and 84% of patients achieved a PASI 75 response following two excimer laser treatments.⁸⁵

In another study of patients with psoriasis (n=40), a 77% improvement in plaque psoriasis was seen after approximately 14 treatments.⁸⁶

Remission rates following excimer laser therapy continue to be examined. In five patients achieving at least a PASI 75 response using excimer laser therapy, a tapering schedule of laser treatment was conducted using one treatment weekly for 1 month, followed by one treatment every 2 weeks for 1 month, and one treatment 4 weeks later. These patients maintained at least a PASI 50 response following the taper period.⁸⁷ Palmoplantar psoriasis has also been treated with the excimer laser in one study (n=54), with complete clearance in 57% of patients following 10-13 laser treatments.⁸⁸

The evidence examining dosage and treatment protocols for excimer laser therapy is extremely limited, and dosage may be guided by induration and scaling of the plaque as well as Fitzpatrick skin type. Treatment protocols have utilized both MED as well as plaque induration. Generally, excimer laser therapy is conducted 2-3 times weekly with at least 48 hours separation between treatments. Side effects consist of erythema, burning, irritation, blistering, and hyperpigmentation of the treated area. Long-term safety with regards to carcinogenesis is not available. Localized phototherapy is considered to be safe in pregnancy although formal studies have not been conducted. One pilot study utilizing excimer laser treatment in children (n=7) had an adverse effect profile similar to that of adults treated with psoriasis, and the excimer laser and other localized treatment devices are generally considered to be safe for use in the pediatric population.⁸⁹

TRADITIONAL SYSTEMIC AGENTS

Methotrexate

Traditional systemic therapies for psoriasis are commonly prescribed for patients with more extensive psoriasis (i.e. more than 10% BSA affected, or for patients with debilitating symptoms secondary to psoriasis). Methotrexate is one of the oldest systemic therapies, and worldwide is the most commonly prescribed systemic medication for the treatment of psoriasis. Methotrexate was initially approved by the FDA for the treatment of psoriasis in 1972. This agent functions by inhibiting dihydrofolate reductase, an enzyme involved in the synthesis of cofactors necessary for the production of nucleic acids. Methotrexate affects rapidly dividing cells, and it is thought to inhibit the proliferation of lymphoid tissue at low weekly doses.⁹⁰ Recently, consensus guidelines on the use of methotrexate were published by the National Psoriasis Foundation.⁹¹

There have been three recent studies examining the efficacy of methotrexate for psoriasis. In one blinded comparison trial (n=90), methotrexate and cyclosporine were compared at 12 weeks. The PASI 75 response was 60% for the methotrexate group and 71% for the cyclosporine

group; the average dose of methotrexate was not stated.⁹² Another recent randomized study compared methotrexate and cyclosporine in 68 patients, with no placebo arm.⁹³ In the cyclosporine group, the average PASI improvement was 72% as compared to 58% in the methotrexate group; the mean dose of methotrexate was not stated. In the CHAMPION study, Saurat et al. conducted a double-blind, controlled study comparing methotrexate to adalimumab, including a separate placebo arm (n=250).⁹⁴ The PASI 75 response after 16 weeks was 80% in the adalimumab treatment group, as compared to 36% in the methotrexate arm and 19% in the placebo arm. Notably, the dosage of methotrexate initially was 7.5 mg for 2 weeks, then 10 mg for 2 weeks, 15 mg for 4 weeks and could subsequently be titrated upwards depending on clinical response. Furthermore, after 8 weeks of treatment, subjects who had achieved a PASI 50 response in the methotrexate group did not have any further increase in dosage, and the overall mean dose of methotrexate was 19 mg. The efficacy of methotrexate may have been greater with a longer duration of treatment.

One possible toxicity from methotrexate usage is elevated liver function tests and commonly, minor elevations of liver enzymes are seen. According to current recommendations, if the elevation exceeds 2x normal, clinicians should check liver function tests more frequently.⁹¹ If the elevation exceeds 3x normal, consider reducing methotrexate dosage, and if the elevation exceeds 5x normal, discontinue methotrexate.⁹¹ Other toxicities can include: anemia, aplastic anemia, thrombocytopenia, leukopenia, nausea, vomiting, diarrhea, fatigue, interstitial pneumonitis, fever, chills, gastrointestinal ulceration, photosensitivity, decreased resistance to infection and alopecia.⁹¹

Regarding liver biopsies, clinicians can first determine whether a patient is considered high or low risk for hepatotoxicity secondary to methotrexate. Risk factors for hepatotoxicity may include a history of greater than moderate alcohol consumption, persistent abnormal liver chemistry laboratory findings, history of hepatitis B or C, diabetes mellitus, obesity, previous exposure to hepatotoxic drugs, family history of an inheritable liver disease and hyperlipidemia.⁹¹ For patients considered low-risk, a baseline liver biopsy is not necessary and a first biopsy is recommended following 3.5-4 g cumulative methotrexate dosage.⁹¹ For high-risk patients, consider a baseline biopsy with subsequent biopsies following 1-1.5 g methotrexate ingestion.⁹¹ It should be noted that some dermatologists choose not to recommend liver biopsies for their patients, as well as many rheumatologists who treat patients with methotrexate.

Methotrexate is recommended for severe psoriasis which has not responded adequately to other therapies such as topical treatment. It is administered as a single oral dose weekly, which is titrated upwards to achieve an optimal response but should not exceed 30 mg/week.⁹⁵ An initial test dose of 2.5-5 mg is recommended and baseline monitoring should include blood count and liver function

tests. Folic acid supplementation of 1-5mg daily except for the day on which methotrexate is taken can be used.⁹⁵ Methotrexate is absolutely contraindicated for patients with the following: alcoholic liver disease, alcoholism, chronic liver disease, immunodeficiency syndromes, leukopenia, thrombocytopenia, and bone-marrow hypoplasia.⁹⁵ Methotrexate is both teratogenic and an abortifacient and is pregnancy category X. Its use is contraindicated in pregnant women, nursing mothers, and in women attempting to conceive.⁹⁵

Cyclosporine

Cyclosporine was originally used as an immunosuppressant in organ transplant recipients since the early 1970s, with efficacy for psoriasis first described in 1979.⁹⁶ Cyclosporine binds to cyclophilin, leading to calcineurin inhibition and decreased levels of inflammatory cytokines such as interleukin-2.⁹⁷ Cyclosporine is rapidly and consistently effective, making it particularly helpful for psoriasis crisis management.

Cyclosporine leads to a PASI 75 response in 50-70% of patients at a dosage of 3 mg/kg/day.⁹⁸ Cyclosporine dosed between 2.5 to 5 mg/kg/day for 12 to 16 weeks can lead to dramatic improvement in psoriasis in 80-90% of patients.⁹⁹⁻¹⁰¹ In one randomized trial of intermittent cyclosporine treatment lasting up to 12 weeks (n=400), patients were either abruptly discontinued from cyclosporine or had cyclosporine dosage gradually tapered.¹⁰¹ The average time to relapse was 113 days for patients who had tapered off treatment at 1 mg/kg/week and 109 days for those who had abruptly stopped treatment. The short cyclosporine courses were generally tolerated well. In another study of patients (n=217) treated with cyclosporine at 1.25-5 mg/kg/day for 6-30 months, 12.5% of patients were maintained on a dosage of 1.25 mg/kg/day without experiencing loss of efficacy.¹⁰²

The most serious toxicities associated with cyclosporine include hypertension and nephrotoxicity.¹⁰³ While observed renal impairment is often reversed following cyclosporine discontinuation, long-term therapy with cyclosporine can lead to permanent kidney damage and decrease in renal function.^{104,105} Renal impairment can be either acute or chronic, where increased glomerular fibrosis may result from a longer duration of treatment and increasing dosage.⁹⁵ Additionally, cyclosporine usage may put patients at increased risk for the development of nonmelanoma skin cancers, specifically squamous cell carcinomas; this risk may be particularly increased in patients who have received previous PUVA treatments.¹⁰⁶ Regarding internal malignancies, patients with psoriasis treated with cyclosporine do not have a significantly increased risk as compared to the general population, but the study conducted was not sufficiently statistically powered to rule out a potential increased risk of malignancy.¹⁰⁷ Patients with uncontrolled kidney disease, hypertension, and history of malignancy

are not considered appropriate candidates for cyclosporine. Other toxicities may include the following: headaches, paresthesias, gingival hyperplasia, acne, nausea, vomiting, myalgias, hypertrichosis, fatigue, hypomagnesemia, hyperkalemia, hyperbilirubinemia, increased risk of infection and increased risk of lymphoproliferative disorders.⁹⁵

Cyclosporine is indicated for adults with severe, recalcitrant psoriasis who are not immunocompromised, although some guidelines suggest the use of cyclosporine for moderate to severe psoriasis. Furthermore, cyclosporine is effective for erythrodermic, generalized pustular and palmoplantar psoriasis.⁹⁵ Recommended dosing is between 2.5-5.0 mg/kg/day in two divided doses, decreasing the dose by 0.5-1.0 mg/kg when psoriasis has cleared or if toxicities have been observed.⁹⁵ In the United States, cyclosporine is approved for 1 year of continuous treatment and outside of the United States for 2 years of continuous usage. Cyclosporine may be initiated again after an intermittent rest period.

Recommended monitoring at baseline includes: blood pressure x2, BUN and creatinine x2, urinalysis, liver function enzymes, CBC, magnesium, potassium, lipid profile, uric acid and possible pregnancy test.⁹⁵ Patients should be monitored carefully for renal toxicity with monthly serum creatinine levels, and the package insert recommends that an elevation of serum creatinine greater than 25% should lead to a 25-50% decrease in cyclosporine dose.^{108,109} Cyclosporine is pregnancy category C and has been associated with decreased duration of pregnancy and lower birth weight in patients who were receiving cyclosporine for transplantation, but does not appear to be teratogenic. The efficacy and safety of cyclosporine in children with psoriasis has not been formally established.

Acitretin

Oral retinoids are derivatives of vitamin A and affect epidermal differentiation and proliferation. Acitretin is the active metabolite of etretinate and has been used for the treatment of psoriasis since 1988. In clinical trials, various dosages have been used and the efficacy and side effects of acitretin are dose dependent. In one study, the average PASI improved by 70-75% after 3 months of acitretin treatment; patients had been treated with 40 mg daily for 4 weeks followed by an individually adjusted dose for the subsequent 8 weeks.¹¹⁰ In another study, 23% of patients treated with 50 mg/day of acitretin for 8 weeks achieved a PASI 75 response.¹¹¹ In a study of 59 patients, acitretin was initiated at a dose of 20 mg daily and increased by 10 mg every 2 weeks until a dosage of 70 mg was reached.¹¹² While 41% of patients experienced marked improvement or clearance of psoriasis, more than a third of patients withdrew from the study because of adverse events. In a study of patients with plaque psoriasis, after 6 months of continuous treatment, 75% of patients had reached PASI 50 and after 1 year of continuous treatment, 88% of patients still in the study

had reached PASI 50 response.¹¹³ Etretinate, the pro-drug of acitretin, has reported usage in erythrodermic psoriasis.¹¹⁴ Acitretin is considered a safe and effective treatment in psoriasis patients who are HIV-positive because it is not considered to be significantly immunosuppressive.¹¹⁵ Furthermore, acitretin is considered to be a rapidly effective treatment for pustular psoriasis, with efficacy in 84% of patients with generalized pustular psoriasis.¹¹⁶

Potential toxicities associated with acitretin can include the following: alopecia, xerosis, xerophthalmia, dry mouth, cheilitis, paresthesias, paronychia, headaches, pseudotumor cerebri, depression, nausea, myalgias, increased liver function tests, and hypertriglyceridemia.⁹⁵ The more commonly observed side effects include mucocutaneous dryness and increased triglycerides. Overall, low-dose acitretin at 25 mg/day is better tolerated by patients compared to 50 mg/day.

Acitretin is approved by the FDA for adults with severe plaque psoriasis and recommended dosing is 10-50 mg/day (lower doses should be used to minimize risk of side effects). Importantly, when acitretin is added while a patient is receiving UV phototherapy, the UV light dose should be reduced by 30-50%.⁹⁵ Baseline monitoring recommended includes lipid profile, liver function enzymes, renal function tests, CBC, and possible pregnancy test.⁹⁵ Acitretin is a systemic retinoid and is pregnancy category X. It is a potent teratogen and is absolutely contraindicated in women of childbearing potential.⁹⁵ Its use in the pediatric population has not been studied and safety has yet to be established.

NONTRADITIONAL SYSTEMIC AGENTS

Nontraditional systemic agents include azathioprine, hydroxyurea, leflunomide, mycophenolate mofetil, sulfasalazine, tacrolimus, and 6-thioguanine. None of these agents are currently approved by the United States FDA for the treatment of psoriasis. The available evidence for efficacy in psoriasis is limited, and these drugs have a variety of toxicities (Table 15-1).

Azathioprine is a purine analogue which blocks purine synthesis, and is commonly used as an immunosuppressant agent for renal transplantation. Azathioprine has been used off label for blistering disease, atopic dermatitis, and psoriasis. Hydroxyurea is an antimetabolite, which is thought to function by inhibiting DNA replication. The major dose-limiting side effect is hematologic toxicity; hydroxyurea is often useful when methotrexate is contraindicated because of liver disease. Leflunomide is a disease-modifying antirheumatic medication which has been used in the treatment of psoriasis and is indicated for rheumatoid arthritis. It inhibits pyrimidine biosynthesis but is more complicated to use than is methotrexate. Mycophenolate mofetil is approved as an immunosuppressive agent for prophylactic treatment in organ transplant recipients. It is the pro-drug of mycophenolic acid which interferes with T-cell proliferation by blocking de novo synthesis

TABLE 15-1—Nontraditional Systemic Agents

Agent	Evidence for Treatment of Psoriasis	Potential Toxicities ⁹⁵
Azathioprine	In one study, 19/29 patients experienced a PASI 75 response ¹¹⁷ In another study, 5/10 patients had >25% reduction in psoriasis ¹¹⁸	Bone marrow suppression, malignancy, squamous cell carcinomas, increased risk of infection, hepatitis, pancreatitis
Hydroxyurea	In one study 55% of patients had a 70% reduction in PASI score after 36 weeks ¹¹⁹ In one study comparing methotrexate to hydroxyurea, patients had a 48% reduction in PASI score at 3 months ¹²⁰	Bone marrow suppression, gastrointestinal symptoms, dermatologic reactions, temporary impairment of renal tubular function, pulmonary fibrosis, neurologic disturbances
Leflunomide	In a randomized controlled trial of 190 patients, 17% of patients had a PASI75 response compared to 8% in the placebo group ¹²¹	Nausea, diarrhea, weight loss, severe liver injury, pancytopenia, thrombocytopenia, agranulocytosis,
Mycophenolate Mofetil	In a study of 23 patients, mean reduction of 47% in PASI score at 12 weeks with patients treated 1-1.5g BID ¹²² In a study of 11 patients treated with 1g BID for 3 weeks followed by 0.5g BID for 3 weeks, there was 47% reduction in PASI score was at 6 weeks ¹²³	Diarrhea, nausea, vomiting, leukopenia, anemia, thrombocytopenia, dysuria, increased incidence of infections, progressive multifocal leukoencephalopathy, hypercholesterolemia, electrolyte disturbances, peripheral edema
Sulfasalazine	In a randomized controlled trial, 7/17 patients experienced moderate improvement in psoriasis after 8 weeks of 3-4g/day treatment compared to 1/27 patients in placebo group ¹²⁴	Anorexia, headache, oligospermia, nausea, vomiting, pruritus, rash, fever, urticaria, hemolytic anemia
Tacrolimus	Patients dosed at 0.05mg/kg had no difference from placebo after 3 weeks, but when dosed at 0.1-0.15mg/kg, there is a significant improvement in PASI score compared to placebo at 9 weeks ¹²⁵	Tremor, headache, diarrhea, nausea, hypertension, abnormal kidney function results
6-Thioguanine	Retrospective, open-label study of 40 patients showed 78% achieved complete or almost complete clearing of psoriasis – dosage schedules and amounts varied widely ¹²⁶	Liver toxicity, increased liver function tests, myelosuppression, hyperuricemia, photodermatitis, gastric ulcers, aphthous ulcers, nonmelanoma skin cancer, taste changes, herpes zoster

BID, twice a day; PASI, psoriasis area sensitivity index.

of guanine nucleotides. Sulfasalazine is thought to have anti-inflammatory properties and is frequently used in the treatment of inflammatory bowel disease; although it has limited efficacy, it is not associated with the organ toxicities associated with methotrexate and cyclosporine. Tacrolimus is a macrolide antibiotic indicated for prophylaxis in organ transplant recipients; it functions as a calcineurin inhibitor. Topical use is described above. Oral tacrolimus can be used similar to cyclosporine. Finally, 6-thioguanine is a metabolite of azathioprine which has been used in the treatment of inflammatory bowel disease; a major concern with this drug is the potential for inducing hepatic vein thrombosis.

BIOLOGIC AGENTS

The biologic agents are proteins produced either through recombinant technology or extracted from animal tissue, and can be used for the treatment of psoriasis. There are five biologic agents which are FDA approved for psoriasis, with one recently withdrawn by the manufacturer. Notably, the data evaluating the safety and efficacy of biologics for psoriasis is based on studies of adults age 18 and older with the single exception of etanercept, which has been evaluated in the pediatric age group.¹²⁷

Alefacept

Alefacept is a recombinant dimeric fusion protein in which the extracellular portion of lymphocyte function-associated antigen (LFA)-3 is linked to the Fc region of human IgG1. Alefacept inhibits activation and decreases the number of memory-effector CD45 RO+ cells.¹²⁸

In the phase III trials, alefacept was administered at 15 mg/week intramuscularly, and 21% of patients achieved a PASI 75 response by week 14 after a 12-week dosing period.¹²⁹⁻¹³² The endpoint for these studies was at 14 weeks, but the maximum response to alefacept was generally observed approximately 6-8 weeks following the last intramuscular injections. Patients who respond to alefacept initially may achieve further benefit through successive treatment courses, each lasting 12 weeks. Patients who achieved a PASI 75 response to alefacept maintained at least a 50% reduction in PASI for a median of 7 months.¹²⁸ Furthermore, patients who experienced at least a 50% improvement in PASI score also had a significant improvement in the Dermatology Life Quality Index as compared to placebo.¹²⁸ There is currently no way to predict which patients may improve significantly with alefacept therapy.

Alefacept is recommended for patients with moderate to severe psoriasis, administered by a 15 mg intramuscular

injection weekly for 12 weeks with a 12 week follow-up nontreatment period.¹²⁷ Patients beginning treatment with alefacept should have a baseline CD4 lymphocyte count with repeated monitoring every other week, and alefacept should not be administered whenever the CD4 count decreases below 250 cells/mL.¹³³ It is recommended that alefacept treatment be discontinued if the CD4 count remains below this threshold for 4 weeks continuously.¹³³ Alefacept is contraindicated in patients infected with HIV; however it should be noted that HIV-positive patients were not included in the phase III pivotal trials.¹²⁷ Alefacept is pregnancy category B.

Efalizumab

Efalizumab is a recombinant humanized monoclonal IgG1 antibody which is directed against the CD11a subunit of LFA-1. This agent interferes with activation and trafficking of T-lymphocytes.¹³⁴ Efalizumab dosage is administered subcutaneously at an initial dose of 0.7 mg/kg followed by 1mg/kg thereafter.¹³⁵ Based on the phase III clinical trials, between 27-39% of patients achieved a PASI 75 response following 12 weeks of treatment with efalizumab.^{134,136,137} Furthermore, after 24 weeks of efalizumab treatment, 44% of patients achieved a PASI 75 response.¹³⁸ In a randomized, placebo-controlled trial, efalizumab was effective for hand and foot psoriasis.¹³⁹

However, by April 2009, there were three confirmed and one unconfirmed but suspected case of progressive multifocal leukoencephalopathy among patients who had been receiving efalizumab treatment continuously for at least 3 years.¹⁴⁰ Three of the cases had resulted in death. Progressive multifocal leukoencephalopathy (PML) is a rare and progressive demyelinating disease which is caused by activation of the JC virus; it is usually fatal, and there is no effective treatment currently available. Efalizumab was thus pulled from the market by European and Canadian regulatory agencies, and subsequently was voluntary pulled from the United States market by its manufacturer Genentech, Inc. in April 2009.¹⁴⁰ As of June 2009, efalizumab is no longer available in the United States.

Adalimumab

Adalimumab is a human antitumor necrosis factor α (TNF- α) monoclonal antibody. Adalimumab binds to both soluble and membrane-bound TNF- α and prevents its interaction with TNF receptors on the cell surface.¹⁴¹ Currently, adalimumab is approved by the FDA for psoriasis, juvenile rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and adult rheumatoid arthritis. Dosing for psoriasis is initiated with an 80 mg subcutaneous loading dose followed 1 week later by a 40 mg subcutaneous dose and then a 40 mg dose subsequently every 2 weeks.¹⁴²

In the pivotal phase III clinical trial evaluating the safety and efficacy of adalimumab (n=1212), patients received adalimumab or placebo for the first 16 weeks of the study.¹⁴³ By week 16, 71% of patients in the adalimumab treatment arm versus 7% in the placebo group had achieved a PASI 75 response. Patients who maintained a PASI 75 response through week 33 were re-randomized 1:1 to receive either adalimumab or placebo. This period of the trial from weeks 33 through 52 was designed to examine the duration of treatment effect and compare the proportion of patients in each group who lost adequate response. Loss of adequate response is defined specifically as an increase in PASI score by 6 points in addition to a loss of PASI 50 response. The percentage of patients rerandomized to placebo who lost adequate response was 28%, compared to 5% in the patients who continued adalimumab treatment. Although rebound of psoriasis typically does not occur following discontinuation of adalimumab, clearance of psoriasis is better maintained with its continuous use.

Potential toxicities of adalimumab include the following: painful injection site reactions in up to 15% of patients, rare reports of serious infections such as tuberculosis and opportunistic infections, rare reports of malignancy, multiple sclerosis, drug-induced lupus (without neurologic or renal complications), and exacerbation of congestive heart failure.¹²⁷ Recommended monitoring at baseline includes a purified protein derivative (PPD) test, liver function enzymes, CBC, and hepatitis screening. Yearly PPD, periodic CBC, and periodic liver function tests can be considered. An evidenced-based review of laboratory monitoring found that only PPD testing was well supported by evidence.¹⁴⁴ Adalimumab is pregnancy category B.¹²⁷

Etanercept

Etanercept is a recombinant human TNF- α receptor fused with the Fc portion of IgG1. It binds to both soluble and membrane-bound TNF- α molecules and thus functions as a TNF- α antagonist.¹⁴⁵ Currently, etanercept is approved by the FDA for moderate to severe plaque psoriasis, rheumatoid arthritis, juvenile rheumatoid arthritis, psoriatic arthritis and ankylosing spondylitis. Etanercept is dosed at 50 mg subcutaneously twice weekly for 12 weeks followed by 50 mg weekly continuously thereafter.

In a phase III trial evaluating the efficacy of etanercept, 34% of patients achieved a PASI 75 response at week 12 after receiving 25 mg twice weekly, and 49% of patients achieved a PASI 75 response after receiving 50 mg twice weekly, compared to 4% in the placebo group.^{146,147} After 24 weeks of treatment, a PASI75 response was observed in 59% of patients receiving 50 mg twice weekly.¹⁴⁶ Notably, some patients will have a loss of clinical response during the step-down period at 12 weeks when the dose is reduced from 50 mg twice weekly to 50 mg weekly. In clinical

practice, some dermatologists pursue continued treatment at 50 mg twice weekly if a patient no longer clinically responds to weekly dosing and if the patient's insurance agrees to cover this dosing regimen. However, etanercept is not indicated for this dosage schedule, such dosing is considered off-label, and is not cost effective compared to other options. Etanercept discontinuation typically does not result in rebound of psoriasis.¹⁴⁷

There has been one clinical study examining the safety and efficacy of etanercept in the pediatric population; no other reports of the use of biologic agents for psoriasis in children were reported.¹⁴⁸ Etanercept was administered once weekly at 0.8 mg/kg, up to a maximum of 50 mg, in children and adolescent patients ages 4-17 years with plaque psoriasis. In this group, 57% of patients achieved a PASI 75 result compared to 11% in the placebo group.

Toxicities associated with etanercept are similar to those associated with adalimumab and include the following: mild pruritus at the injection site, rare cases of serious infections such as tuberculosis, rare cases of malignancy, drug-induced lupus, multiple sclerosis, exacerbation of congestive heart failure, and cytopenia.¹²⁷ Baseline monitoring recommended is a PPD test, liver function enzymes and CBC; a yearly PPD and periodic CBC and liver function tests can be considered.¹²⁷ Etanercept is pregnancy category B and is contraindicated in septic patients.¹²⁷

Infliximab

Infliximab is a murine-human chimeric antibody, which is composed of a human IgG1 region and a mouse variable region.¹⁴⁹ Infliximab binds to both transmembrane and soluble TNF- α molecules. Currently, infliximab is approved by the United States FDA for use in treating psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, Crohn's disease, and ulcerative colitis. Unlike the other TNF- α inhibitors, infliximab is administered as an intravenous infusion. Typically, it is dosed at 5 mg/kg for 2 to 3 hours at weeks 0, 2, 6 and then every 8 weeks subsequently for the treatment of psoriasis.¹⁵⁰ In the phase II trials, approximately 80% of patients achieved a PASI 75 response by week 10 following 3 intravenous doses of infliximab.¹⁵¹ Furthermore, after 10 weeks of therapy, there was a 91% improvement in the Dermatology Life Quality Index.¹⁵² Patients who receive continuous treatment with infliximab not only achieve a better clinical response as compared to patients who receive intermittent therapy, but these patients are also less likely to develop antichimeric antibodies against infliximab.¹⁵²⁻¹⁵⁵ Some clinicians administer low-dose methotrexate to patients in order to decrease the formation of antibodies against infliximab.¹⁵⁶ Infliximab has continued efficacy and during the pivotal phase III trial, 61% of patients had maintained a PASI 75 response by week 50, after nearly a year of therapy at 5 mg/kg with 8-week intervals.¹⁵⁶

Toxicities associated with infliximab include serum sickness and infusion reactions (which occur more frequently in patients who have developed anti-drug antibodies), rare malignancies including hepatosplenic T-cell lymphoma in adolescents, rare cases of serious infections such as tuberculosis, drug-induced lupus, multiple sclerosis, exacerbation of congestive heart failure and new onset of congestive heart failure.¹²⁷ The majority of infusion reactions, which occur in approximately 16% of patients, consist of mild urticaria and pruritus, but some patients experience chest pain, shortness of breath, hypertension, and rarely anaphylaxis.¹²⁷ As infusion reaction risk correlates with the presence of antichimeric antibodies; patients treated with methotrexate, or other immunosuppressive therapies tend to have a lower incidence of infusion reactions.¹²⁷ Recommended monitoring at baseline includes PPD, liver function tests, CBC and hepatitis screening; consider a yearly PPD examination and periodic CBC and liver function tests.¹²⁷ Infliximab is contraindicated in patients with New York Heart Association class III or IV congestive heart failure, at the dosage of 5 mg/kg or greater.¹²⁷ Infliximab, like the other biologic agents previously discussed, is pregnancy category B.

Tumor Necrosis Factor- α Inhibitors

The TNF- α antagonists have been used in the treatment of inflammatory diseases for over a decade and are being used with increasing frequency for the treatment of plaque psoriasis. General recommendations pertaining to the class of TNF- α antagonists have been established by an American Academy of Dermatology work group of psoriasis experts, with regards to adverse events and monitoring for patient safety.¹²⁷

Due to reports of tuberculosis reactivation, tuberculosis testing through a PPD test should be performed at baseline on all patients who will be treated with an anti-TNF agent.¹⁵⁷ TNF antagonists are contraindicated in patients with active, serious infections and should not be used with live vaccines. Hepatitis B reactivation following treatment with TNF inhibitors has been reported and all patients should be screened for hepatitis B infection at baseline. TNF antagonists should not be used in patients with multiple sclerosis or other demyelinating diseases. These agents should not be used in first-degree relatives of patients with multiple sclerosis based on evidence that they have a potentially increased risk of developing multiple sclerosis (sibling relative risk between 18-36).¹⁵⁸ TNF blockers should be used with caution in patients with congestive heart failure, and it is recommended that patients with New York Heart Association class III or IV avoid use of any TNF inhibitor.¹⁵⁷ Patients with New York Heart Association class I or II congestive heart failure who have an ejection fraction of <50% should also avoid use of any TNF inhibitor.¹⁵⁷

SYSTEMATIC REVIEWS AND RECOMMENDATIONS

With the wide variety of psoriasis treatment options available—all with different side effect profiles, practicability, and cost—systemic reviews and treatment guidelines are needed to help educate patients on the relative risks and benefits of treatment, to support physicians' treatment decision-making, and to inform other parties (payers and regulators) about appropriate treatment paradigms Tables 15-2 and 15-3.

For topical psoriasis therapies there has been one large systematic Cochrane review in 2002 by Mason et al. which found that topical Vitamin D, corticosteroids, dithranol and tazarotene were more effective than placebo. It also found no significant difference in head-to-head comparisons of Vitamin D agents against topical corticosteroids. Moreover, combined treatment with Vitamin D with corticosteroids performed significantly better than Vitamin D alone, or corticosteroid alone.¹⁵⁹

Current guidelines reflect these findings accordingly. The current U.S. guidelines set out by Menter et al. graded the evidence on an I-III scale, and made clinical recommendations based on the best available evidence from grade A-C. Grade A recommendations were based on consistent and good-quality patient-oriented evidence, grade B recommendations were based on inconsistent or limited-quality patient-oriented evidence, and grade C recommendations were based on consensus, opinion, or case studies. A grade A recommendation was given to the combination use of a topical vitamin D analogue with a topical corticosteroid. Other recommended topical treatments with grade A recommendations included corticosteroids, tazarotene, and vitamin D analogues. Tacrolimus, pimecrolimus and coal tar were supported by grade B recommendations.¹⁹ Canadian guidelines also recommend calcipotriol, and calcipotriol/betamethasone dipropionate combination.¹⁶⁰

In Europe, Nast et al. published S3-Guidelines for Germany that also recommended topical corticosteroids, vitamin D analogs, and their combination. Tazarotene and dithranol were also recommended, however dithranol was only recommended during hospitalization and neither was recommended nor discouraged for outpatient treatment. Calcineurin inhibitors were also neither recommended nor discouraged. Coal tar use, however, was highly inadvisable for use as monotherapy or in combination therapy. As opposed to the U.S.'s grade B recommendation. The use of coal tar, according to the German recommendations, is obsolete with only one, albeit poor, study evaluating the efficacy for monotherapy, which did not show any statistically significant difference from placebo. They further cited that coal tar is carcinogenic (especially when combined with UV light), and is not desirable for patients because of its color and odor.¹⁶¹

For phototherapy, the guidelines for the US, Canada, and Europe are all relatively similar. The U.S. guideline

found oral PUVA, and combination of PUVA with topical or systemic agents supported by a grade A recommendation. Narrowband UVB therapy and excimer laser therapy are recommended with a grade of B. And, the combination of UVB with topical agents, systemic agents, or biologic agents are also recommended with grade of B. Broadband UVB therapy is recommended with grade of C.¹⁶² The Canadian guidelines recommend PUVA phototherapy with grade B and UVB phototherapy recommended with grade D.¹⁶⁰ The European S3-Guidelines recommend narrowband UVB as first choice for induction therapy for moderate to severe psoriasis vulgaris. PUVA is next choice if UVB is not effective, but not for long-term treatment. Excimer lasers are advised to be limited to the targeted treatment of individual psoriatic plaques.¹⁶³ German S3-Guidelines highly recommended phototherapy as an induction therapy, and recommended excimer lasers for targeted treatment of individual psoriatic plaques. Phototherapy was neither recommended nor discouraged for combination use with dithranol and corticosteroids. However, phototherapy was not recommended for long-term treatment, or for combination with topical vitamin D3 analogs.¹⁶¹

Systemic treatments, both with traditional and biologics, have been the focus of many systematic reviews. A recent meta-analysis comparing the systemic agents, published by Warren et al. in 2010, found that several traditional nonbiologic systemic therapies have equal or superior efficacy to some biologic therapies. For example, fumaric acid esters and cyclosporin were found to be more effective than efalizumab. Meta-analyses comparing some of the biologic therapies for psoriasis showed that for short-term treatment efficacy (10–16 weeks): infliximab, etanercept 50 mg twice weekly, etanercept 25 mg twice weekly, efalizumab, alefacept. Rates of adverse events, however, were significantly higher with infliximab, efalizumab, and alefacept than with placebo.¹⁶⁴

Despite the findings of this meta-analysis, the U.S. guidelines gave grade A recommendations for the biologics (adalimumab, etanercept, infliximab, alefacept, and efalizumab), while methotrexate, cyclosporine, sulfasalazine, tacrolimus and acitretin were given grade B recommendations.^{165,166} Azathioprine, mycophenolate mofetil and 6-thioguanine were given grade C recommendations.¹⁶⁶ In Canada, the biologics (adalimumab, infliximab, etanercept, alefacept) are also recommended with grade A. Cyclosporine was also recommended, but with grade B.¹⁶⁰

European guidelines differ from North American countries in their use and recommendation for fumaric acid esters, and for their disapproval of acitretin. In the European S3-Guidelines both fumaric acid esters and cyclosporine were recommended for induction in moderate to severe psoriasis vulgaris. Fumaric acids were also recommended for use in combination with topical treatments. Methotrexate recommendations were mixed because of the limited evidence available. Retinoids were not recommended as a first choice for monotherapy. Adalimumab, etanercept, and infliximab were only recommended for

TABLE 15-2—Recent Systematic Reviews and Guidelines for Psoriasis Therapy

Article	Focus	Methodology	Limitations
Mason et al. Topical Treatments for Chronic Plaque Psoriasis: Cochrane Review	Focus on topical therapies for psoriasis	The Cochrane database, EMBASE, MEDLINE, Science Citation Index, National Research Register were all searched through 2005. Review included 131 RCTs with 21,448 participants.	Studies evaluated were typically approximately 6 weeks long, while in clinical practice patients use topical agents for months to years. Few long-term studies evaluating topical agents are available.
Menter et al. Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis	Section 3: Treatment of Psoriasis with Topical Therapies	An evidence-based model was used to search the MEDLINE database from 1960-2008. Evidence was graded on a 3-point scale and clinical recommendations made with grade of A, B, or C.	Few randomized, controlled studies are available for evaluating coal tar therapy and in comparing different topical agents in the treatment of psoriasis.
Menter et al. Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis	Section 5: Phototherapy and Photochemotherapy	An evidence-based model was used to search the MEDLINE database from 1960-2009. Evidence was graded on a 3-point scale and clinical recommendations made with grade of A, B, or C.	Limited and conflicting data available regarding combination of Vitamin D agents with phototherapy. Limited data on use in the pediatric population, but UVB therapy generally considered a second-line therapy for pediatric psoriasis patients who fail topical therapies. No data on systemic PUVA in pediatric populations, may be used with caution in patients under 18 years old.
Menter et al. Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis	Section 4: Treatment of Psoriasis with Systemic Agents	An evidence-based model was used to search the MEDLINE database from 1960-2008. Evidence was graded on a 3-point scale and clinical recommendations made with grade of A, B, or C.	Limited literature available regarding the use of methotrexate and cyclosporine in pediatric population. Cyclosporine use during pregnancy based on data from patients undergoing organ transplantation (not psoriatic patients); cyclosporine pregnancy category C.
Smith et al. British Association of Dermatologists Guidelines for Use of Biological Interventions in Psoriasis 2005	Review current anti-TNF and anti-T cell biologic therapies approved for psoriasis in the UK	Literature review performed on EMBASE and MEDLINE from 1990 through 2005 for clinical trials involving etanercept, infliximab and efalizumab; scoring performed for strength of evidence.	Conclusion regarding efalizumab was made prior to published reports of association with long-term efalizumab use and progressive multifocal leukoencephalopathy. Only efalizumab, infliximab and etanercept were evaluated (adalimumab, alefacept were not licensed in the UK at time of review).
Papp et al. Canadian Guidelines for the Management of Plaque Psoriasis	Evaluation of topical agents, systemic agents, biologics and phototherapy for psoriasis	Scottish Intercollegiate Guidelines Network used to evaluate over 5000 peer-reviewed articles and assign strength of recommendations.	Guideline committee with potential conflict of interest. Ten industry supporters funded the guidelines.
Menter et al. Guidelines of Care for the Management of Psoriasis and Psoriatic Arthritis	Section 1: Biologic Therapies for Psoriasis	An evidence-based model was used to search the MEDLINE database from 1990-2007. Evidence was graded on a 3-point scale and clinical recommendations made with grade of A, B, or C.	Guttate, pustular, inverse, erythrodermic psoriasis subtypes not considered in this analysis. Conclusion regarding efalizumab was made prior to published reports of association with long-term efalizumab use and progressive multifocal leukoencephalopathy.

Article	Focus	Methodology	Limitations
<p>Pathirana et al. European S3-Guidelines on the systemic treatment of psoriasis vulgaris and</p> <p>Pathirana et al. On the development of the European S3 guidelines on the systemic treatment of psoriasis vulgaris: structure and challenges.</p>	<p>Guidelines for systemic treatments of psoriasis vulgaris</p>	<p>Medline, EMBASE, and the Cochrane Library were searched from May 2005 to October 2007 for efficacy of the systemic treatments of plaque psoriasis. Studies were appraised by one methodologist using a standardized literature evaluation form (LEF), and later by a member of the dEBM. If the two appraisals differed, the study was reassessed. 678 studies were evaluated, 114 fulfilled inclusion criteria. Levels of evidence were graded on a 4-point scale and clinical recommendations made with PASI 75 results</p> <p>A list of key questions concerning the different systemic therapies was compiled and graded (using a DELPHI procedure) by the guidelines group and distributed to the authors of the individual chapters who answered questions. Some of the more important questions were also subject to consensus consisting of a nominal group process and a DELPHI procedure. A passage was regarded as consented when $\geq 75\%$ of the voting experts agreed. There was external review by experts according to the AGREE recommendations, and by European dermatological societies according to the EDF Standard Operation Procedure.</p>	<p>Possible conflict of interest that may have influenced the outcomes of the guidelines. Further, there was limited editorial independence from the funding body. Total time for developing the guidelines took 44 months due to extensive internal and external review.</p>
<p>Warren et al. What's new in psoriasis? Analysis of the clinical significance of systematic reviews on psoriasis published in 2007 and 2008.</p>	<p>Summarizes 6 systematic reviews on psoriasis published from January 2007 to October 2008</p>	<p>PubMed, MEDLINE, EMBASE were searched using a systematic review filter. Also searched were The Cochrane Library, the Database of Abstracts of Reviews of Effects (DARE) and the Health Technology Assessment Database and of the NLH Skin Disorders Specialist.</p>	<p>Only six systematic reviews met inclusion criteria.</p> <p>Limited studies on appropriate use of screening and monitoring tests with biologics (currently, they are neither supported nor refuted)</p> <p>Limited studies evaluating the effectiveness of existing psychological interventions in psoriasis.</p>
<p>Nast et al. Evidence-based (S3) guidelines for the treatment of psoriasis vulgaris and</p> <p>Nast et al. Evidence-based (S3) guideline for the treatment of psoriasis vulgaris - Update: "Therapeutic options" and "Efalizumab"</p>	<p>To develop evidence-based guidelines for the management of psoriasis, specifically induction therapy in cases of mild, moderate, and severe plaque-type psoriasis in adults. Update adjusts guidelines for efalizumab (Raptiva) for which the European Medicines Agency (EMEA) recommended suspension as of February 19, 2009.</p>	<p>Systematic search of the literature was conducted in May 2005. 6,224 publications searched and 142 studies fulfilled the inclusion criteria. Studies assessed using a literature evaluation form (LEF). Levels of evidence were graded on a 4-point scale. Guidelines were developed following the recommendations of the AWMF. Guidelines Group defined important sections as passages requiring consensus. These were discussed and approved following formal consensus processes (Nominal Group Technique) in the framework of the consensus conferences. An expert group who evaluated treatment efficacy, level of evidence, safety, practicability, and cost/benefit ratio developed the therapeutic recommendations. Recommendations were then finalized during interdisciplinary consensus conferences.</p> <p>Efalizumab (Raptiva) guidelines changed with the guideline group consenting by way of Delphi method</p>	<p>Some treatments with strong strength of recommendations had LOE level 3 and 4.</p> <p>No S3 guidelines for adalimumab or ustekinumab included in the update (in 2010 a complete revision is expected which will include these 2 drugs).</p>

TABLE 15-3—Guidelines for Childhood Psoriasis Treatment and Complementary Medicine

Article	Focus	Methodology	Major Conclusions	Limitations
de Jager et al. Efficacy and safety of treatments for childhood psoriasis: A systematic literature review.	Systematically review treatment efficacy and safety in childhood psoriasis. Propose a recommendation for topical and systemic treatment.	PubMed, EMBASE, and the Cochrane Controlled Clinical Trial Register were searched for efficacy and safety of all treatment options in childhood psoriasis and a level of evidence was determined. 64 studies could be included, describing 646 children in total. Of these 64 studies, only 6 were RCTs.	Calcipotriene (grade A) +/- topical corticosteroids (grade C) is treatment of choice for mild to moderate childhood psoriasis. For treatment-resistant flexural and/or facial psoriasis, tacrolimus 0.1%, grade C, can be added. If this treatment regimen is not effective, or if psoriasis is moderate to severe, treatment with dithranol, grade C, is recommended. NB-UVB, grade C, can be considered in adolescents for short duration after above treatments fail. Antibiotics, grade C, can be considered in case of guttate psoriasis and suspicion of a streptococcal infection. MTX, grade C, is the systemic therapy of choice. Retinoids, grade C, can be used for pustular and erythrodermic psoriasis for short-term treatment. Treatment with cyclosporine, grade C, should only be used in exceptional cases. Etanercept, grade A, should be considered as a third-line drug as long-term side effects and risks are unknown	Limited number of RCTs, so all LOEs were included. Most of the evidence is of a low level, grade C and D. Only treatment with vitamin D and etanercept have higher LOE (level A). Most literature concerns induction of remission, rather than maintenance therapy, follow-up period and duration of remission. None of the studies have long-term safety profiles.
Smith et al. Complementary and alternative medicine for psoriasis: a qualitative review of the clinical trial literature.	Review clinical trial literature on complementary and alternative medicine for psoriasis treatment	PubMed, MEDLINE, EMBASE, and AMED (Allied and Complimentary Medicine) were all searched up to January 2008 for randomized, controlled trials in the English language for which clinical response of psoriasis was the primary end point.	No evidence was found for vitamin D, zinc, acupuncture, topical vitamin B12 and avocado oil, or selenium. There was conflicting evidence for aloe vera, fish oil, climatotherapy, and mind/body interventions. Evidence of effect was found with neem, <i>M. aquifolium</i> , inositol among psoriasis taking lithium, and Chinese medicine (all with only one study for support).	Low quality of studies (as assessed by Jadad scores) due to lack of blinding as an inclusion criteria and that most trials used an as-treated analysis rather than an ITT. Only one author determined inclusion of studies and assignment of Jadad scores.

induction therapy, only if the conventional systemic agents were inadequate in response, contraindicated, or not tolerated. Neither alefacept nor efalizumab were recommended as a first choice among the biologics for induction therapy.¹⁶³ Britain's guidelines recommend etanercept, infliximab, and efalizumab for chronic phase psoriasis with strength of recommendation A.¹⁶⁷ Last, the German S3 guidelines also highly recommended fumaric acid esters for long-term therapy, and also made a recommendation for use in induction therapy as well. Other highly recommended medications were etanercept and infliximab for induction therapy. Cyclosporine alone or in combination with topical preparations (vitamin D3 analogs or corticosteroids) was also recommended, although not highly, for induction therapy. Methotrexate was recommended for long-term therapy while acitretin, again, was not recommended because of its lack of efficacy.¹⁶¹

CONCLUSION

Treatment options available for psoriasis vary widely, and it is integral for patients and physicians to work together in building an appropriate treatment plan. Patients are encouraged to use the National Psoriasis Foundation website to learn about classification of psoriasis severity and for a comprehensive list of currently available psoriasis treatments with descriptions. Patients can access educational brochures about both topical and systemic treatments at <http://www.psoriasis.org/netcommunity/learn03>. Patients can also access *It Works For Me*, a unique online resource from the National Psoriasis Foundation which includes hundreds of helpful tips and treatment reports from patients who have successfully managed their psoriasis and/or psoriatic arthritis.

Deciding on a treatment regimen for psoriasis involves several factors. Psoriasis severity will be considered and treatment will depend on the localized versus generalized nature of disease. Mild psoriasis affects <3% BSA, moderate psoriasis affects between 3 to 5–10% BSA and severe psoriasis affects more than 5–10% BSA. Patients with more mild to moderate disease (localized) may be managed with topical treatment, whereas patients with moderate to severe (generalized) psoriasis will consider topicals as adjunct treatment to phototherapy, acitretin, methotrexate, cyclosporine, and biologic agents. Physicians must additionally consider the location of a patient's psoriasis (i.e., hands, feet, genitals, face) and its effect on quality of life.

Patient adherence to treatment will influence the efficacy of a particular therapy. Involving the patient in decision-making in choosing a particular vehicle for topical medication, or using a combination topical treatment, may improve adherence to a treatment regimen. The best vehicle for topical treatment is ultimately the one which the patient will use. Finally, cost-effective management for extensive disease must also be taken into account. For moderate to severe psoriasis, UVB phototherapy is considered the best first-line option, with or without the addition of acitretin, followed by PUVA, methotrexate, and the biologic agents.

What We Know

- Topical agents including corticosteroids, vitamin D analogues, tazarotene, tacrolimus, pimecrolimus, coal tar, anthralin, and salicylic acid have all demonstrated efficacy in the treatment of psoriasis. Special consideration should be given to the strength and duration of use of topical corticosteroids because of the risk of local and systemic side effects.
- Ultraviolet phototherapy (UVB and PUVA) is efficacious for generalized psoriasis and may be considered the most cost-effective treatment for extensive disease, with or without the addition of acitretin.
- Systemic agents including methotrexate, cyclosporine, and acitretin are efficacious in the treatment of psoriasis, and methotrexate is the most cost-effective treatment for generalized psoriasis following phototherapy.
- The biologic agents including infliximab, adalimumab, etanercept, and alefacept have demonstrated efficacy in the treatment of psoriasis. Physicians should follow the recommended monitoring guidelines outlined in this chapter based on AAD consensus guidelines.

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Treatment of Lichen Planus

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Lichen planus (LP) was first defined by Dr. Wilson in 1869 as an inflammatory disorder of the stratified squamous epithelia of unknown etiology.¹ Lichen planus is a relatively common disorder that affects the skin, mucous membranes, nails, hair, and rarely esophagus. Lichen planus is characterized by itchy red-purple papules most commonly on the extremities of middle-aged adults.² Oral LP (OLP) can be the sole clinical presentation of the disease.

CLINICAL SUBTYPES

Cutaneous lichen planus (CLP) has different clinical subtypes: annular, linear, hypertrophic, atrophic, vesiculobullous, palmoplantar, follicular, actinic, and lichen planus pigmentosus. The classic skin lesions of lichen planus are characterized by shiny, red to purple-colored, flat-topped, papules, sometimes showing a small central depression. A thin, transparent, and adherent scale may be located on top of the lesion. Fine, whitish points or lacy lines referred to as Wickham's striae may be present over the surface of well-developed papules.³ OLP mainly has six clinical presentations: erosive, atrophic, papular, reticular, plaque-like, and bullous. OLP typically presents in buccal mucosa (80-90%) with a bilateral white network (reticular) pattern. Reticular OLP is the most common subtype and is usually asymptomatic. Atrophic or erythematous OLP has thinned reddened mucosa with faint white striae. Erosive/ulcerative OLP is the most advanced subtype with a multifocal pattern of distribution. It is clinically important because the lesions are painful. A pseudomembrane sometimes covers the ulcer. Table 16-1 addresses the most common sites of involvement for some subtypes. The pattern of vulvovaginal mucosal LP is similar to OLP. The most significant unfortunate outcome of chronic erosive vulvar LP is scarring. It can cause resorption of the labia minora (agglutination) and clitoral hood, resulting in clitoral burying (68%) and narrowing of the introitus (59%). Scarring and adhesions of the vagina make sexual intercourse impossible.⁴⁻⁶ Figure 16-1 demonstrates different types of LP.

DIFFERENTIAL DIAGNOSIS

Annular lichen planus may resemble granuloma annulare but the latter lacks any scale or Wickham's striae. Mucous membrane pemphigoid has a similar clinical presentation to erosive/ulcerative OLP. The whitish hyperkeratotic striae and presence of skin involvement can be the main differentiating signs.⁷ Vulvar mucosal LP can be mistaken with lichen sclerosis or vulvovaginal blistering diseases and the only ways to distinguish them would be the presence of Wickham's striae or biopsy.

ETIOLOGY AND EPIDEMIOLOGY

Emotional stress, tobacco use, oral or gastrointestinal candidiasis, diabetes mellitus, autoimmune diseases, internal malignancies, dyslipidemia, human papillomavirus (HPV), and hepatitis C virus (HCV) are some of the predisposing and risk factors for LP.² These associations have been strongly proven.

T-cell activation is central to the pathogenesis of lichen planus. Antigen-specific CD8 positive cytotoxic T-cell infiltration in epithelium results in apoptotic basal keratinocytes. Some nonspecific mechanisms may have a partial role in the pathogenesis, including matrix metalloperoxidase activation, mast cell degranulation, basement membrane alteration, and chemokine/cytokine secretion. The main pathologic process in LP is a cell-mediated response in the dermoepidermal junction.⁸ LP induces the activation of helper T lymphocytes in the deeper layers of the skin in the early stages. T helper activation leads to cytokines secretion including interleukin-2, interleukin-6, interleukin-12, interferon gamma, and TNF-alpha and TNF-beta and most importantly chemokine (C-C motif) ligand 5. Unfortunately, the exact etiology remains to be discovered.

The estimated prevalence of LP varies from 0.22% to 5%.⁹⁻¹³ In a paper from Britain, the incidence of LP has been reported as 32-37 per every 100,000 person. It typically affects middle-aged adults of both genders. No sexual

TABLE 16-1—The Most Common Sites of Involvement in LP Based on Subtypes	
	Sites of involvement
Cutaneous Lichen Planus	
Actinic	Sun exposed areas
Atrophic	All parts of body
Erosive	Soles of feet
Follicular	Scalp
Guttate	Trunk
Hypertrophic	Ankles and interphalangeal joints
Linear	Leg – scratched area
Nail disease	Fingernails
Papular	Flexor surfaces
Bullous	Feet
Oral lichen Planus	
Reticular	1- Buccal mucosa and mucobuccal folds 2- Lateral and dorsum parts of tongue 3- Gingiva and vermillion portion of lip
Atrophic	Attached gingiva
Erosive	1- Lateral and Ventral portions of tongue 2- Buccal mucosa
Bullous	Posterior and inferior parts of buccal mucosa

predilection is evident but some reports noted a slight predominance in women (2:1).¹⁴ This is partially unusual for an autoimmune disease and suggests other unknown parallel mechanisms.

Prognosis

Cutaneous lichen planus remits within 6 months to a year but hypertrophic CLP may persist for years if left untreated. Reticular OLP is usually asymptomatic but can have a chronic or progressive nature. The location and severity of the lesions in erosive OLP may change over time with cycles of concurrent healing and lesion formation. Erosive lesions do not heal spontaneously. Patients with erosive OLP or generalized LP have a poor quality of life. Proper and immediate treatment strategies are needed to contain the symptoms and signs for these patients. The association between virus infections (such as HPV and HCV) and LP is a topic of debate. Syrjänen et al.¹⁵ performed a meta-analysis to investigate the role of HPV in OLP patients. The odds ratios for HPV in general and HPV-16 were remarkable and significant [5.12 (95%CI: 2.40-10.93) and 5.61(95%CI: 2.42-12.99, respectively]. This finding provides further evidence that HPV is present in OLP patients more frequently than the normal population and

it may transform OLP into squamous cell carcinoma.¹⁶ Erosive OLP and hypertrophic CLP are the main subtypes with malignant potential. HPV vaccination and/or HPV screening in chronic erosive OLP and hypertrophic CLP cases can be considered.

Moreover, we performed a meta-analysis of all included studies in three previously published meta-analyses¹⁷⁻¹⁹ in addition to five new studies.²⁰⁻²⁴ (Figure 16-2) The included studies evaluated the prevalence of HCV in LP patients and compared it with a control group. Based on data pooling of 64 comparisons, there is a statistically and clinically significant common odds ratio of 5.58 (95% CI, 3.72-8.38) for the study group compared with the control population in favor of the association between LP and HCV. Subgroup analysis based on geographical distribution showed a similar trend reported by Shengyuan et al.¹⁷ Regardless of the nature of the relationship between HCV and LP (association or co-existence), we recommend developing a regional screening protocol for HCV in LP patients. LP patients with evident risk factors for HCV should be screened because serious complications can arise, if left untreated. Additionally, a well-designed prospective cohort study with a proper sample size is needed to establish these relationships.

Methods

Types of Studies

All systematic reviews and all randomized-controlled trials (RCTs) of any design that evaluate the effectiveness of any intervention for cutaneous and/or mucosal (oral and/or genital) lichen planus were considered.

Types of Participants

Studies in which a physician diagnosed cutaneous and/or mucosal lichen planus clinically and/or histopathologically were included. Skin or mucosal involvement in these patients could be the sole presentation or with each other.

Types of Interventions

We included studies that compare at least one active treatment with a control, which may be a placebo, no treatment, or an alternative intervention. We considered all treatments, including but not limited to the following categorized therapies: topical corticosteroids, systemic corticosteroids, retinoids (e.g., acitretin, etretinate, oral isotretinoin, and tretinoin), vitamin D3 analogues (e.g., KH 1060, calcipotriol), topical immunomodulators (e.g. pimecrolimus, tacrolimus), immunosuppressives, phototherapy (e.g., UVA, UVB, PUVA), surgery (cryosurgery, laser therapy), anti-microbials (e.g., metronidazole, griseofulvin,



FIGURE 16-1 A. Reticulated white striae of the lower labial mucosa; B. Reticulated white striae of the buccal mucosa; C. Reticulated white striae of the lower lip proper; D. Confluent reticulated white striae of the lateral tongue; E. Focal erosions of the maxillary attached gingiva.



FIGURE 16-1 (Continued) F. Violaceous papules on the dorsal hand and volar wrist (courtesy of Dr. Omid Zargari); G. Reticulated white striae involving the glans penis (courtesy of Dr. Omid Zargari); H. Hypertrophic lichen planus: centrally eroded hyperkeratotic plaques involving the lower leg; I. Dorsal pterygium of the thumbnail; J. Zosteriform lichen planus: linearly oriented confluent violaceous papules on the arm.

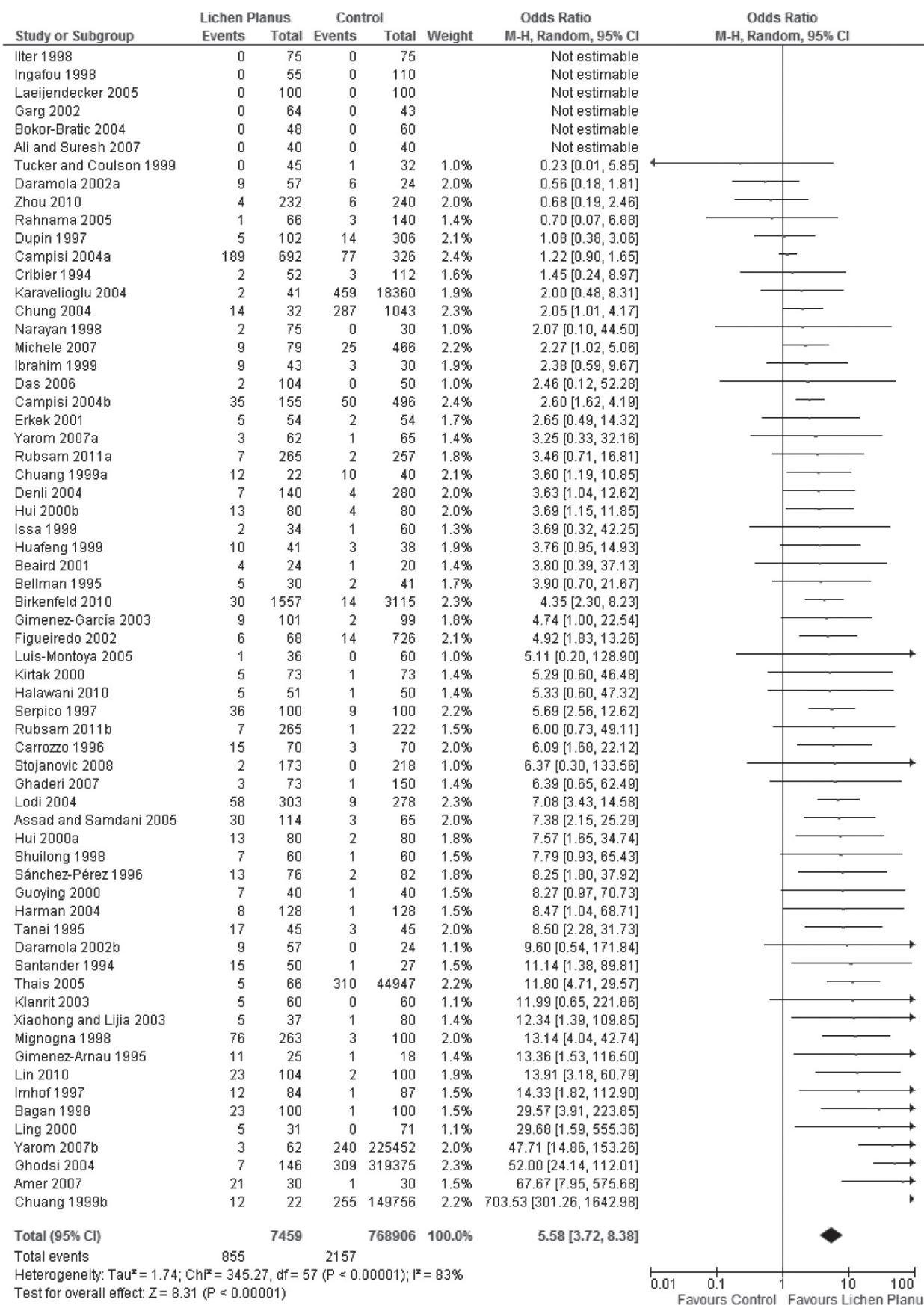


FIGURE 16-2 Meta-analysis of all studies that evaluate the prevalence of hepatitis C among LP patients vs. control populations. Odds ratios were calculated for all relevant studies using Mantel-Haenszel method and random effect model. Complete references are provided as online appendix 1.

miconazole, hydroxychloroquine), biologic therapies (e.g., alefacept, adalimumab), complementary and alternative medicine (e.g., homeopathic medicine, traditional Chinese medicine)

Search Strategy

Pubmed, Medline, and EMBASE were searched using terms: Lichen and Planus

Notice: There is no definitive and immediate cure for LP lesions in many circumstances and this fact makes it challenging for both patients and physicians (dermatologists, dentists, and gynecologists). Life-long clinical follow-up is fundamental.

Seven relevant systematic reviews were found and summarized in Table 16-2. There is no comprehensive recent systematic review that covers all relevant RCTs.

What are the effects of topical and systemic treatments on CLP? (Table 16-3)

Corticosteroids

Corticosteroid medicines are derivatives of the natural corticosteroid hormones that are produced by the adrenal glands. They are the mainstay of LP treatment.

EFFICACY: One randomized trial compared oral prednisolone 30 mg plus topical hydrocortisone-17-butyrate cream to topical hydrocortisone-17-butyrate cream only regimen for 10 days and reported significantly more patients with clinical response with the combined regimen.²⁵

SAFETY: Mild heartburn and euphoria occurred in oral prednisone group but not in topical corticosteroids only

TABLE 16-2—Systematic Reviews of LP

Study	Number of Included RCTs	Period of Literature Search	Diseases Covered	Treatments Covered	Notes
Cribier 1998 ⁷⁶	3	1966-March 1998	Cutaneous and mucosal lichen planus	Retinoids, Phototherapy, Corticosteroids, Griseofulvin, Cyclosporine	No indication of seeking the possibility of meta-analysis, underestimation of relevant RCTs
Al Johani 2009 ⁷⁷	10 (269 patients)	1966-December 2008	Oral lichen planus	Calcineurin inhibitors	All oral diseases were included. Non-English abstracts were considered. Non-randomized studies were considered. Although covered all relevant trials but considered some as non-randomized. No meta-analysis.
Chan 2000 ⁷⁸ & Zakrzewska 2005 ⁷⁹	11 (223 patients)	1966-2007	Oral lichen planus	Cyclosporine, Topical or systemic retinoids, Topical steroids, Phototherapy	Underestimation of relevant RCTs. Gaeta et al. was included although it is not a RCT
Yu-liang 2009 ⁸⁰	14 (358 patients in included English papers)	1966-2007	Oral lichen planus	Cyclosporine, Tacrolimus, Pimecrolimus, Total glucosides of Peony, Corticosteroids, Retinoids, Chitin	Quasi-randomized controlled trials were also included. Underestimation of relevant RCTs.
Zhong-cheng 2008 ⁸¹	3 (72 patients)	1990-2007	Oral lichen planus	Pimecrolimus	Limited to pimecrolimus
Elad 2010 ^{82,83}	16 (588 patients)	1948-2010	Oral lichen planus and other oral mucosal conditions	Pimecrolimus Tacrolimus Cyclosporine Retinoids BCG-PSN	A comprehensive systematic review of all immunomodulators and immunosuppressives. Non-randomized trials were considered too.

BCG-PSN, Polysaccharide nucleic acid fraction of bacillus Calmette-Guerin; RCT, randomized controlled trial.

TABLE 16-3—Treatments of CLP

Study	Design	No. of Patients*	Comparators	Therapy Duration	Efficacy Results	Safety Results	Follow-up Duration	Notes
Kellett, 1990 ²⁵	Randomized double-blind placebo-controlled, single center trial	19 vs. 19 (14 vs. 14)	Oral prednisolone 30 mg plus topical hydrocortisone-17-butryrate cream twice daily vs. placebo daily plus topical hydrocortisone-17-butryrate cream twice daily	10 days	Physician VAS severity, patient VAS severity, median time to clearance 18 weeks vs. 29 weeks, Clinical improvement, p<0.05 for all	Mild heartburn: 1/14 vs. 0/14; Euphoria: 1/14 vs. 0/14 euphoria, p>0.05 for both	2 years	All types of LP, Long term follow-up
Laurberg, 1991 ³⁴	Randomized double-blind placebo-controlled, multi center trial	32 vs. 33 (28 vs. 31)	Three capsules (10 mg) of acitretin vs. placebo daily	8 weeks	Clinical improvement: 18/28 (64.3%) vs. 4/31 (12.9%), p<0.05	Dry lips, cheilitis, dry mouth, dry nose, dry skin, scaling, and hair loss were seen more frequently in acitretin group.	No	CLP (with or without OLP) cases were included. Well explained randomization concealment. No wash-off period between phases of the study. No detectable plasma levels of acitretin.
Omidian 2010 ²⁹	Randomized, double-blind, placebo controlled, single center trial	26 vs. 26 (23 vs. 21)	Oral sulfasalazine vs. placebo at initial doses of 1 g/day increasing 0.5 g per 3 days up to 2.5 g/day	3–6 weeks	Clinical improvement: 21/23 (91.3%) vs. 2/21 (9.5%); pruritus 2/23 (8.7%), vs. 18/21 (85.7%), p<0.05 for both	8/26 (nausea, epigastric pain and diarrhea, mild leukopenia, low grade fever, headache, and skin rash (30.7%)) vs. 0/26 (0%), p<0.05; In sulfasalazine group, 3 left the study due to side effects.	No	Generalized LP
Sehgal 1972 ³¹	Randomized, double-blind, placebo controlled, single center trial	19 vs. 19 (17 vs. 17)	Oral griseofulvin vs. placebo 500 mg/day	4–6 weeks	Clinical improvement: 12/17 (70.6%) vs. 6/17 (35.3%), p<0.05	No side effects	No	CLP

(Continued)

TABLE 16-3—Treatments of CLP (Continued)

Study	Design	No. of Patients*	Comparators	Therapy Duration	Efficacy Results	Safety Results	Follow-up Duration	Notes
Glade 1998 ²⁶	Randomized, double-blind, placebo controlled, single center trial	5 vs. 5	KH1060 1µg/g ointment vs. placebo twice daily	8 weeks	Unclear clinical results (no significant difference)	Burning sensation: 1/5 (20%) vs. 3/5 (60%), p>0.05	No	Chronic idiopathic CLP
Boulou 2000 ²⁷	Randomized, double-blind, placebo controlled, single center trial	49 vs. 43 (38 vs. 36)	KH1060 1µg/g of ointment vs. placebo twice daily	8 weeks	Clinical improvement: 14/38 (36.9%) vs. 15/36 (41.7%), p>0.05	No side effects	4 weeks	Non localized CLP
Theng 2004 ²⁸	Randomized, open label, active controlled, single center trial	15 vs. 16	Calcipotriol 50 mg/g versus betamethasone 0.1% ointments twice daily	12 weeks	Thickness improvement: 7/15 (46.7%) vs. 8/16 (50%), p>0.05	Erythema and pruritus: 7/15 (20%) vs. 0/16 (0%), p>0.05	No	Nonfacial CLP

* The numbers in the parenthesis denote the number of patients per group who finished the study. CLP, cutaneous lichen planus; OLP, oral lichen planus; VAS, visual analogue system.

group.²⁵ Other possible adverse events for topical steroids would be local skin atrophy, or telangiectasis. Long-term application of oral corticosteroids may be avoided or reserved for more severe flare-ups.

LIMITATIONS AND COMMENTS: This is a small RCT that proved beneficial additive effects of oral prednisone to topical corticosteroids therapy. Additionally, the therapy duration was short enough to avoid the development of more serious side effects such as bleeding, seizure, or bone fracture.

Retinoids (Acitretin)

Retinoids have been used in medicine for over 50 years. Acitretin is a second-generation retinoid and is taken orally.

EFFICACY: In the only randomized trial, acitretin was shown to be more efficacious than placebo. Twenty-one out of 32 patients (65.6%) in acitretin group and 8 out of 33 (24.2%) in placebo group had clinical improvement.

SAFETY: In the only published RCT, the adverse events were more frequent in acitretin group (87.5% vs. 51.5%)

LIMITATIONS AND COMMENTS: Women must avoid becoming pregnant for at least 2-3 years after discontinuing acitretin because of birth defect concerns. Acitretin interferes with the action of microdose progestin contraceptive pills. Pregnancy tests should be regularly taken while taking acitretin. Safety and efficacy ratio of acitretin should be considered in LP patients.

Vitamin D analogues

Calcipotriol is a vitamin-D analogue, and has around 1% potency of the natural hormone calcitriol or 1,25 dihydroxycholecalciferol. It is mainly used for psoriasis. Additionally, KH1060 is a potent analogue of 1 alpha, 25-dihydroxyvitamin D3.

EFFICACY: Two randomized placebo-controlled trials evaluated the efficacy of KH1060 in CLP and found no significant benefit.^{26,27} One randomized open label trial compared calcipotriol 50 mg/kg with betamethasone 0.1% ointment and addressed no meaningful difference in efficacy.²⁸

SAFETY: At least based on published randomized trials, there is no major adverse event for KH1060. Calcipotriol patients may have more pruritus or erythema.²⁸

LIMITATIONS AND COMMENTS: There is no evidence to support KH1060 for CLP and evidence for calcipotriol needs reconfirmation.

Sulfasalazine

Sulfasalazine is an anti-inflammatory agent that is extensively used in inflammatory bowel disease especially ulcerative colitis. It is also an alternative therapy for rheumatoid arthritis. The ingested form is not active and would be activated into 5-aminosalicylic acid by colonic bacteria.

EFFICACY: One RCT showed successful treatment of generalized LP with sulfasalazine with an efficacy of 91.3% compared to 9% with placebo.²⁹

SAFETY: In the only RCT, eight patients in the sulfasalazine group experienced adverse effects such as nausea, epigastric pain, truncal skin rash, headache, and fever.²⁹ In an uncontrolled study, 4/20 (20%) of patients discontinued sulfasalazine treatment because of more serious adverse events such as gastric pain, poor glycemic control, fever and cutaneous rash.³⁰

LIMITATIONS AND COMMENTS: Based on current literature, sulfasalazine is remarkably effective but not so safe. It should be reserved for widespread disease or severe flare-ups because of intolerable side effects such as nausea, epigastric pain, and fever.

Griseofulvin

EFFICACY: Sehgal et al. found 70.6% efficacy for griseofulvin versus 35.3% for placebo in the only randomized study.³¹ It is in contradiction with the finding of Massa and Rogers that Griseofulvin was a better option for OLP but not for cutaneous lesions.³²

SAFETY: Sehgal et al. reported no side effects for griseofulvin.³¹ This is in contradiction with other studies that reported some side effects in up to 50% of patients.³³

LIMITATIONS AND COMMENTS: Based on the only randomized trial, griseofulvin is an effective drug for LP³¹ but based on other non-randomized studies, the efficacy of this drug is under question.^{32,33}

What are the effects of topical corticosteroids on mucosal LP? (Table 16-4)

Topical corticosteroids are known as first line therapy for LP. They are preferred over systemic corticosteroids, except during acute exacerbations based on expert opinions.

EFFICACY: Nine RCTs were identified for topical steroids. In one trial, triamcinolone acetonide mouthwash was compared to its commercially available 0.1% paste. The

TABLE 16-4—Oral and Topical Corticosteroids for Mucosal LP

Study	Design	No. of Patients*	Comparators	Therapy Duration	Efficacy Results	Safety Results	Post Treatment Follow-up Duration	Notes
Oral Corticosteroids								
Malhorta, 2008 ⁴³	Randomized, open label, active-controlled single center trial	25 vs. 24	5 mg of betamethasone orally for 2 consecutive days per week vs. topical triamcinolone acetonide (0.1%) paste thrice	3+3 months	Good to excellent response: 17/25 (68.0%) vs. 16/24 (66.0%); Symptom-free state 13/25 (52%) vs. 12/24 (50%), relapse 9/23 (39.1%) vs. 5/23 (21.7%), p>0.05 for all	14/25 (56.0%) vs. 6/24 (25.0%), p=0.05	No	Symptomatic OLP, The change in the quality of life with treatment was not measured
Topical Corticosteroids								
Cawson, 1968 ³⁶	Randomized double-blind active-controlled, single center trial	30 vs. 18	Betamethasone valerate (0.1 mg) pellets vs. hydrocortisone (2.5 mg) pellets, QID	4 weeks	Significant improvement: 20/30 (66.6%) vs. 3/18 (16.6%), p<0.05	Candidiasis: 4/30 (13.3%) vs. 0/18 (0%), P>0.05	Up to 3 years (No Follow-up in betamethasone group)	No randomization concealment. In hydrocortisone group, Randomized and non-randomized patients have been mixed.
Tyldesley, 1977 ³⁵	Randomized double-blind placebo-controlled, single center trial	12 vs. 11 (11 vs. 9)	Betamethasone valerate vs. placebo, 2 puffs, QID (0.8 mg)	8 weeks	Moderate to good treatment response: 8/11 (72.7%) vs. 2/9 (22.2%), p<0.05	Candidiasis: 8/11 (72.7%) vs. 7/9 (77.7%), p>0.05. One case of acute pseudomembranous Candidiasis in active group	No	Diagnosis was mainly based on clinical manifestations.
Hegarty, 2002 ³⁷	Randomized, open label, active controlled, single center, crossover trial	22 vs. 22	Fifty µg two-dose unit fluticasone propionate sprays vs. betamethasone sodium phosphate mouthrinse (500 µg), each 4 times daily	6 weeks	Symptomatic improvement (VAS): 15.3 (95% CI:7.8 to 22.8) vs. 11.0 (95% CI:3.8 to 18.2); OHIP: 3.9 (95% CI:1.2 to 6.7) vs. 3.7 (95% CI:0.4 to 7.1; OHQoL: 4.5 (95% CI:1.4 to 7.5) vs. 4.1 (95% CI:1.4 to 6.7), p>0.05 for all	Nausea: 4/22 (18.1%) vs. 0/22 (0%); Bad taste and smell: 6/22 (27.2%) vs. 0/22 (0%); Dry mouth: 2/22 (9.0%) vs. 0/22 (0%) P>0.05 for all	No	Erosive ulcerative OLP
Campisi, 2006 ⁵⁴	Randomized, observer-blinded, parallel group active-controlled clinical single center trial	20 vs. 30 (18 vs. 27)	Clobetasol-17-propionate ((lipid-loaded microspheres 0.025%) compared with clobetasol-17-propionate (lipophilic ointment in a hydrophilic phase 0.025%)	1 month (twice daily) + 1 month (once daily)	VAS pain score (0-100): 22.9 ±21.3 vs. 33.5± 19.5, p=0.05; Clinical improvement: 14/17 (82.4%) vs. 24/28 (85.7%), p>0.05; Appropriate patient compliance: 14/17 (82.3%) vs. 24/28 (85.7%), p>0.05	acute oral candidiasis 1/17 (5.9%) vs. 2/28 (7.1%), p>0.05	5 months	Atrophic-erosive lichen planus ; Appropriate follow-up visits

(Continued)

Carbone, 2009 ³⁹	Randomized, double-blind, placebo-controlled single center trial	18 vs. 17 (15 vs. 15)	Clobetasol propionate 0.025% vs. clobetasol propionate 0.05% twice daily	2 months	No side effects	Atrophic erosive OLP; The patients of both groups received anti- myotic prophylaxis (miconazole 2% gel once daily plus chlorhexidine 0.12% mouth rinse without alcohol 3 times daily).		
	Muzio, 2001 ⁴⁰	Randomized, double-blind, active-controlled single center trial	8 vs. 8 vs. 8	Clobetasol propionate 0.05% ointment 3 times daily vs. clobetasol propionate 0.05% in an adhesive denture paste twice daily vs. clobetasol propionate 0.05% in an oral analgesic base (Orabase-B) twice daily	Up to 15 days	Candidiasis: 1/18 (5.5%) vs. 7/18 (38.9%) vs. 2/18 (11.1%), p<0.05	No	OLP (mainly erosive/ ulcerative)
Ungphaihoon 2005 ³⁴	Randomized, open label, active controlled single center trial	11 vs. 9	Triamcinolone acetonide 0.1% mouth-wash vs. triamcino-lone acetonide 0.1% paste four times daily	4 weeks (1- 16 weeks)	Symptom improvement in, 4 weeks: 10/11 (90.9%) vs. 9/9 (100%); Sign improvement: 10/11 (90.9%) vs. 9/9 (100%), p>0.05 for both	Candidiasis: 0/11 (0%) vs. 2/9 (22.2%), p>0.05	Unclear	Symptomatic OLP
Buajeeb, 2000 ⁴²	Randomized, open-label, active- controlled, single center trial	15 vs. 15 vs. 18	Fluocinolone acetonide 0.1% gel (with carbopol resin 1% vs. 0.5%) vs. fluocinolone acetonide in orabase 0.1% four times daily	4 weeks	Clinical improvement: 13/15 (86.6%) vs. 13/15 (86.6%) vs. 15/18 (83.3%), p>0.05	Candidiasis: 0/15 (0%) vs. 0/15 (0%) vs. 1/18 (5.5%), p>0.05	No	Erosive/atrophic OLP included
Voute 1993 ⁴¹	Randomized, double-blind, placebo- controlled, single center trial	20 vs. 20	Fluocinonide 0.025% ointment vs. placebo 6 times daily	9 weeks	Sign improvement: 16/20 (80%) vs. 6/20 (30%), p<0.05; sign improvement for erosive OLP: 10/14 (71.4%) vs. 6/13 (46.1%), p>0.05; Symptom improvement: 18/20 (90%) vs. 12/20 (60%), p=0.06	No side effects	No	OLP

* The numbers in the parenthesis denote the number of patients per group who finished the study.
QID, four times a day; OLP, oral lichen planus; VAS, visual analogue system OHQoL, oral health impact profile; OHQoL, oral health quality of life.

results were comparable in improving signs and symptoms.³⁴ Betamethasone valerate aerosol had remarkable clinical improvement in 72.7% of patients, whereas placebo achieved 22.2%.³⁵ On the other hand, betamethasone valerate pellets were found to be superior to hydrocortisone pellets (66.6% vs. 16.6%, respectively).³⁶ Furthermore, betamethasone sodium phosphate mouth rinse was comparable to fluticasone propionate spray in a 6-week clinical trial in terms of symptomatology improvement, McGill pain score, oral health impact profile and quality of life.³⁷ Clobetasol-17-propionate is a superpotent corticosteroid. Two different formulations of Clobetasol-17-propionate including lipid-loaded microspheres 0.025% and lipophilic ointment in a hydrophilic phase 0.025% were compared with each other. Both had similar efficacy, except for the ability to alleviate pain with the former formulation worked better.³⁸ In another RCT, 0.025% and 0.05% concentrations of clobetasol propionate were evaluated. Both concentrations had remarkable effects on erosive-atrophic OLP. Relapse occurred more frequently with the lower concentration.³⁹ Muzio et al. investigated three different preparations of clobetasol propionate (0.05% ointment three times daily versus 0.05% in an adhesive denture paste twice daily versus 0.05% in Orabase-B twice daily) for erosive-ulcerative OLP. They found that clobetasol propionate in an adhesive denture paste would have the best efficacy results.⁴⁰ Voute et al. addressed the remarkable clinical efficacy of fluocinonide 0.025% in adhesive paste in a randomized placebo-controlled study.⁴¹ It was shown that fluocinolone acetonide gel 0.1% in two different base forms and fluocinolone acetonide 0.1% in orabase has similar efficacy and safety.⁴²

SAFETY: Candidiasis is the most common adverse effect. Some studies did use antimycotic agents to prevent fungal oral infections and that is the reason for inconsistent results. In a study, Muzio et al. addressed the fact that candidiasis occurs more frequently with clobetasol propionate in an adhesive denture paste as oppose to the other forms.⁴⁰ Nausea and dry mouth can develop with more potent topical steroids. Longer durations of therapy can cause more serious local effects such as skin atrophy.

LIMITATIONS AND COMMENTS: Betamethasone valerate and fluocinonide 0.025% ointment are the only topical corticosteroid that has been compared with placebo for OLP.

What are the effects of systemic corticosteroids on mucosal LP? (Table 16-4)

EFFICACY: Malhotra et al.⁴³ randomized the patients to receive either oral mini-pulse therapy of betamethasone 5 mg for

2 consecutive days weekly or triamcinolone acetonide (0.1%) paste thrice daily for 3 months followed by stepwise tapering during the next 3 months. Symptomatology cure was achieved in 52% versus 50% of patients, respectively. Good to excellent clinical response was noted in 68% versus 66% of patients, respectively.

SAFETY: Patients on mini pulse therapy of oral beta-methasone had more side effects (56%) in comparison with triamcinolone acetonide paste (25%), P<0.05.⁴³

LIMITATIONS AND COMMENTS: There is not enough evidence-based literature to support the idea of using systemic corticosteroids for mucosal LP. This study shows evidence that oral mini-pulse corticosteroid therapy can be as effective as topical triamcinolone paste. Betamethasone oral mini-pulse treatment can achieve clinical response faster than topical medication but with more safety concerns and quicker relapse. Hence, it may help to alleviate severe flare-ups.

What are the effects of calcineurin inhibitors on mucosal LP? (Table 16-5)

Calcineurin inhibitors (immunomodulators) belong to the azomycin class of macrolactam immunosuppressives, acting by the inhibition of T-cell activation via the calcineurin pathway and inhibition of the release of numerous inflammatory chemokines, and therefore acting as anti-inflammatory and immunomodulator agent. The mechanism of action of pimecrolimus and tacrolimus is similar but it is more selective for pimecrolimus as it has no effect on dendritic (Langerhans) cells.⁴⁴ It has lower permeation through the skin than topical steroids or topical tacrolimus, although they have not been compared with each other for their permeation ability through mucosa.⁴⁵ On the other hand, tacrolimus is more potent.

Pimecrolimus

EFFICACY: Four placebo-controlled RCTs⁴⁶⁻⁴⁹ were appraised for pimecrolimus 1% cream with a total of 72 evaluable erosive OLP patients. Pimecrolimus is at least more effective than placebo in curing the erosive lesions (odds ratio of 10.41 [95% CI, 1.84-58.97], P=0.008), but not necessarily in improving symptoms such as VAS pain scores (mean difference of 0.42 [95% CI, -2.11-2.95], P>0.05). On the other hand, pimecrolimus was as effective as triamcinolone acetonide paste according to one study.⁴⁵

SAFETY: Meta-analysis of all four studies revealed that burning sensation occurs more frequently with pimecrolimus than placebo (odds ratio of 7.67 [95% CI, 1.24-47.36], P=0.03) or triamcinolone acetonide.⁴⁵

TABLE 16-5—Calcineurin Inhibitors for Mucosal LP

Study	Design	No. of patients*	Comparators	Therapy Duration	Efficacy Outcomes [†]	Safety Results	Post Treatment Follow-up Duration	Notes
Swift 2005 ⁴⁸	Randomized, double-blind, vehicle-controlled, single-center trial	10 vs. 10	Pimecrolimus 1% cream vs. placebo	4 weeks	Ulceration (area, mm ²), Erythema (area, mm ²), VAS discomfort score	1/10 (10%, burning sensation) vs. 0/10 (0%), P>0.05	No	Erosive OLP, Short treatment duration
Passeron 2007 ⁴⁷	Randomized, double-blind, vehicle-controlled, single-center trial	6 vs. 6	Pimecrolimus 1% cream vs. placebo	4 weeks	Mean physician assessment	2/6 (33.3%, burning sensation) vs. 0/6 (0%), P>0.05	Not clear	Erosive OLP, Small sample size, Short treatment duration, Detectable pimecrolimus plasma levels
Volz 2008 ⁴⁹	Randomized, double-blind, vehicle-controlled, single-center trial	10 vs. 10	Pimecrolimus 1% cream vs. placebo	4 weeks	Investigator's global assessment, Ulceration, Erythema	5/10 (50%, 4 burning sensation cases), vs. 1/10 (10%, no burning sensation cases), P>0.05	4 weeks (only responding patients)	Erosive OLP, Short treatment duration
McCaughay 2010 ⁴⁶	Randomized, double-blind, vehicle-controlled, single-center trial	10 vs. 11 (8 vs. 11)	Pimecrolimus 1% cream vs. placebo	6 weeks	Investigator's global assessment: Pain, erythema, erosion	Drug-related adverse event 0/10 (0%) vs. 1/11 (9%), p>0.05	No	Erosive OLP, Detectable pimecrolimus plasma levels in 9 out of 10 cases
Gorouhi 2007 ⁴⁵	Randomized, investigator-blind, active-controlled, single-center trial	20 vs. 20 (18 vs. 17)	Pimecrolimus 1% cream vs. triamcinolone acetonide 0.1% paste QID	8 weeks	VAS pain score, Oral Health Impact Profile score, Thongprasom Clinical score	2/20 (10%, burning sensation) vs. 0/20 (0%), P>0.05	8 weeks	OLP; Pimecrolimus plasma levels were not measured. Assessor blind only. Chlorhexidine mouthrinse were added to prevent candidiasis
Laeijendecker 2006 ⁵²	Randomized active-controlled, single center trial	20 vs. 20	Tacrolimus 0.1% ointment vs. triamcinolone acetonide 0.1%	6 weeks	Clinical improvement	8/20 (40%) vs. 3/20 (15%), p>0.05; Recurrent headaches were reported.	Mean: 14-15 months	Symptomatic OLP, No Evidence of study blindness, No measurement of tacrolimus plasma level

(Continued)

TABLE 16-5—Calcineurin Inhibitors for Mucosal LP (Continued)

Study	Design	No. of patients*	Comparators	Therapy Duration	Efficacy Outcomes[†]	Safety Results	Post Treatment Follow-up Duration	Notes
Corrocher 2008 ⁵¹	Randomized double-blind active-controlled, single center trial	16 vs. 16	Tacrolimus 0.1% ointment vs. clobetasol propionate 0.05% ointment four times daily	4 weeks	Median pain score, Median score of burning, sensation, Median mucosal extension	9/16 (56.2%, transient burning sensation) vs. 0/16 (0%), p<0.05	2 weeks	Moderate to severe OLP, Short duration of treatment Undetectable plasma levels of tacrolimus.
Radfar 2008 ⁵⁰	Randomized double-blind active-controlled, single center trial	15 vs. 15	Tacrolimus 0.1% ointment vs. clobetasol 0.05%, ointment [#]	6 weeks	0–10 pain VAS score, Lesion size, Clinical response	No side effects	9 months	Erosive/ulcerative OLP; Nystatin oral rinse was applied to prevent candidiasis.
Eisen 1990 ⁵³	Randomized double-blind placebo-controlled, single center trial	8 vs. 8	Cyclosporine 0.1% moth rinse (1500 mg/day) vs. placebo	8 weeks	Erythema, Erosions, Reticulation, Symptoms (pain)	16/16 (100%, Burning sensation) vs. 8/8 (100%, Burning sensation), Precipitation of the solution: 12/16 (75%) vs. 3/8 (37.5%), P>0.05 for both	Up to 6 months	Symptomatic OLP; Plasma levels of cyclosporine reached to 150 ng/ml; Small sample size
Conrotto 2006 ⁵⁴	Randomized double-blind active-controlled, single center trial	20 vs. 20	Cyclosporine 1.5% ointment (26 mg/day) vs. clobetasol 0.025% ointment, twice daily	8 weeks	Clinical improvement, Symptomatology	Adverse events: 6/20 (30%) vs. 1/20 (5%), p<0.05	8 weeks	Atrophic/eruptive OLP; Plasma levels of cyclosporine were undetectable; Miconazole gel and chlorhexidine mouthrinse were added to prevent candidiasis.
Yoke 2006 ⁸⁵	Randomized active-controlled, single center trial	68 vs. 71	Cyclosporine 0.1% solution vs. triamcinolone acetonide 0.1% in orabase 3 times daily	8 weeks	Clinical improvement	14/68 (20.5%, Burning sensation) vs. 3/71 (4.2%, p<0.05); GI problems: 4/68 (5.8%) vs. 0/68 (0%, p>0.05); One case of swelling and itching of lips was reported in cyclosporine group.	No	Plasma levels of cyclosporine reached to 340 ng/ml. Randomization concealment was clearly stated. Blindness is not clear.

Sieg 1995 ⁸⁶	Randomized investigator-blind active-controlled, single center trial	6 vs. 7	Cyclosporine 0.1% solution vs. triamcinolone acetonide 0.1% in orabase 3 times daily	6 weeks	Clinical Improvement, Complete response	0/6 (0%) vs. 3/7 (42.8%, Burning sensation), p>0.05	One year	One patient with abnormal plasma levels of cyclosporine due to swallowing the drug; Small sample size; The results were not reported explicitly.
Thongprasam 2007 ⁸⁷	Randomized blind active-controlled, single center trial	6 vs. 7	Cyclosporine 0.1% solution vs. triamcinolone acetonide 0.1% in orabase 3 times daily	8 weeks	Clinical improvement	4/6 (66.6%, Burning sensation) vs. 0/7 (0%); Gastrointestinal discomfort, Breast tenderness, Dizziness, Itching, swelling lips, and Petechial Hemorrhages	One year	One patient with transient abnormal plasma levels of cyclosporine; Small sample size Comparability of the baseline data is uncertain.

* The numbers in the parenthesis denote the number of patients per group who finished the study.

† Efficacy results have been presented in Figures 14-3, 14-4, and 14-5.

‡ 4 times/day for 2 weeks followed by 3 times/day for 2 weeks, 2 times/day for 1 week, and 1 timer/day for 1 week CLP, cutaneous lichen planus; QID, four times a day; OLP, oral lichen planus; VAS, visual analogue system.

LIMITATIONS AND COMMENTS: Pimecrolimus is effective in erosive OLP with limited transient side effects (burning sensation). Its effect size can reach as high as triamcinolone paste. Future studies should focus on maintenance therapy of chronic refractory OLP with this agent and document its safety profile. Moreover, it is important to compare pimecrolimus and tacrolimus in the treatment of mucosal LP.

Tacrolimus

EFFICACY: Two RCTs compared tacrolimus 0.1% with clobetasol propionate 0.05% ointment.^{50,51} Based on data pooling, tacrolimus improve the signs of OLP better than clobetasol propionate (15.84 [0.12, 85.20], p=0.0009). Another RCT, evaluated the efficacy of tacrolimus 0.1% ointment to triamcinolone acetonide 0.1%. Tacrolimus was more potent than triamcinolone (clinical improvement: 90% vs. 45%, respectively).⁵²

SAFETY: Corrocher et al. reported 56.2% and 0% side effects in tacrolimus and clobetasol groups, respectively.⁵¹ A similar trend was observed when tacrolimus was compared to triamcinolone (40% vs. 15%, respectively).⁵² Radfar et al. found no side effects in either group.⁵⁰ Meta-analysis of data showed inconsistent results in this regard.

LIMITATIONS AND COMMENTS: Burning sensation is the main side effect. It resolves quickly and is noted more frequently with tacrolimus than topical corticosteroids. Tacrolimus is more potent than clobetasol in terms of clinical improvement. Tacrolimus is recommended as second line therapy for mucosal LP lesions with limited response to corticosteroids.

Cyclosporine

Cyclosporine was initially isolated from the fungus *tolypocladium inflatum* isolated from a soil sample obtained by Sandoz scientists at Hardangervidda, Norway in 1969.

EFFICACY: There are five RCTs for cyclosporine in treatment of mucosal LP. The routine dose of cyclosporine was 100 mg/mL. Cyclosporine showed improvement in pain, erosion, reticulation, and erythema when compared to placebo.⁵³ When compared to clobetasol, cyclosporine was less effective (65% vs. 95%). However, cyclosporine and clobetasol had similar effects on symptom relief.⁵⁴ Three studies investigated the efficacy and safety of cyclosporine and triamcinolone acetonide 0.1% in orabase. The relatively higher efficacy of triamcinolone is established (odds ratio of 0.46 [95% CI, 0.25-0.87], p=0.02) in addition to fewer side effects (odds ratio of 10.88 [95% CI, 3.34-35.41], P<0.0001).

SAFETY: Burning sensation, swelling, and itching of the lips are the most common symptoms.

LIMITATIONS AND COMMENTS: Although it has been shown in one trial that cyclosporine is better than placebo, triamcinolone and clobetasol were proven to be more effective than cyclosporine.

What are the effects of retinoids on mucosal LP? (Table 16-6)

Isotretinoin

EFFICACY: Two relevant RCTs were recognized. Isotretinoin 1% gel and placebo gel improved the clinical signs in 90% and 10% of OLP patients, respectively.⁵⁵ Scardina et al. compared two concentrations of isotretinoin gel (0.18% and 0.05%). They did not differ significantly with regards to symptom relief, however, the higher concentration cured the erosions in 74.3%, whereas the 0.05% gel had the same effect in 25.7% of patients.⁵⁶

SAFETY: Burning, stinging, superficial desquamation, erythema^{55,56} and photosensitivity can occur.

LIMITATIONS AND COMMENTS: Efficacy of isotretinoin gel on erosions is inconsistent and needs further confirmation.

Tretinoin

EFFICACY: One placebo-controlled RCT noted a significantly higher cure rate in tretinoin 0.1% group.⁵⁷ In a pseudo-randomized trial, tretinoin 0.05% was compared to fluocinolone acetonide 0.1%. Fluocinolone was superior to tretinoin for clinical improvement and pain, however, they were comparable for the treatment of erosive lesions.⁵⁸

SAFETY: Oral dryness and irritation were reported.⁵⁸

LIMITATIONS AND COMMENTS: Tretinoin 0.1% may be considered as an alternative.

Etretinate

Etretinate was approved by the FDA in 1986 for severe psoriasis.

EFFICACY: One placebo-controlled RCT showed remarkable clinical response in etretinate group.⁵⁹

SAFETY: Severe side effects were observed in six patients (out of 23). Side effects of chopped lips and dry skin occurred in all etretinate treated patients. Furthermore, etretinate increased ALT levels in three patients.⁵⁹

LIMITATIONS AND COMMENTS: Etretinate was subsequently removed from the United States market in 1998 because of the high risk of birth defects and it is not recommended.

TABLE 16-6—Retinoids for Mucosal LP

Study	Design	No. of Patients*	Comparators	Therapy Duration	Efficacy Results	Safety Results	Post Treatment Follow-up Duration	Notes
Oral Retinoids								
Hersl 1982 ⁵⁹	Randomized double-blind placebo-controlled, single center, cross-over trial	14 vs. 14 (10 vs. 14)	Etretinate 75 mg vs. placebo daily	8 weeks	Clinical improvement: 12/14 (85.7%) vs. 2/25 (8%), p<0.05	Severe side effects: 6/23 (26%) vs. 0/14 (0%), p<0.05; Dry cheilitis plus dry scaly skin: 23/23 (100%) vs. 0/14 (0%) p<0.05; Increased ALAT levels: 3/23 (13%) vs. 0/14, (0%), p>0.05	3 months	Non-responsive OLP
Topical Retinoids								
Scardina 2006 ⁵⁶	Randomized open label, active-controlled, single center trial	35 vs. 35	Isotretinoin 0.18% gel vs. isotretinoin 0.05% gel twice daily	3 months	Disappearance of erosive/atrophic lesions: 26/35 (74.3%) vs. 9/35 (25.7%), p<0.05; 0-10 pain VAS score: 0 vs. 4, p>0.01	No side effects except transient increased burning sensation and pain within 30 minutes after drug application	10 years (ongoing)	OLP
Giustina 1986 ⁵⁵	Randomized double-blind placebo-controlled, single center trial	11 vs. 11 (10 vs. 10)	Isotretinoin 0.1% gel vs. vehicle gel twice daily	8 weeks	Clinical improvement (0-5 scale): 9/10 (90%) vs. 1/10 (10%), p<0.05; Symptom free: 5/6 (83%) vs. 3/6 (50%), p>0.05	Transient burning in all patients in both groups, Superficial desquamation and erythema with isotretinoin group	No	OLP; Well explained randomization, concealment, No detectable plasma levels of isotretinoin, Less impressive results for erosive OLP.
Boisnic 1994 ⁵⁷	Randomized double blind, placebo-controlled, single center trial	10 vs. 10	Tretinoin 0.1% ointment vs. placebo ointment twice daily	4 months	Clinical improvement after 2 months: 8/10 (80%) vs. 5/10 (50%), p>0.05; clinical improvement after 4 months: 9/10 (90%) vs. 4/10 (40%), p=0.05; Complete cure after 2 months: 3/10 (30%) vs. 1/10 (10%), p>0.05; Complete cure after 4 months: 7/10 (70%) vs. 1/10 (10%), p<0.05	Generally transient burning sensation in both groups with 2 patients with dry mouth, p>0.05%	4 months	OLP; Erosive cases were excluded. No detectable plasma levels of isotretinoin.

* The numbers in the parenthesis denote the number of patients per group who finished the study. OLP, oral lichen planus; VAS, visual analogue system.

What are the effects of aloe vera on mucosal LP? (Table 16-7)

Aloe vera Linne is a succulent from the Aloe family. The use of aloe vera is being promoted for a large variety of conditions.

EFFICACY: Three randomized placebo-controlled trials were found in this regard. Choonhakarn et al.⁶⁰ and Salazar-Sanchez et al.⁶¹ assessed aloe vera in OLP and Rajar et al.⁶² in vulvar LP. We pooled the data for clinical response (odds ratio of 20.85 [95% CI, 7.79-55.81], p<0.00001). There is a significant trend toward effectiveness of aloe vera in comparison with placebo for mucosal LP.

SAFETY: In all three trials, only two patients in the aloe vera group encountered an adverse event and the meta-analysis showed no difference between aloe vera and placebo (odds ratio of 5.39 [95%CI, 0.25-117.77], p>0.05)

LIMITATIONS AND COMMENTS: There is no standard dose of aloe vera for mucosal LP. Rajar et al. published the only randomized trial for vulvovaginal LP.⁶²

What are the effects of other treatments on LP? (Table 16-8)

PUVA

PUVA is a combination therapy that consists of psoralen treatment plus UVA exposure. It is mainly used for psoriasis and vitiligo

EFFICACY: One randomized open label within patient trial compared the effects of PUVA therapy with control. After 12 sessions of PUVA therapy, the lesions remarkably healed (81.7%) compared to the control lesions (37.5%).⁶³

SAFETY: PUVA causes limited systemic adverse events like nausea, dizziness, photosensitivity, headache, and paresthesia.

LIMITATIONS AND COMMENTS: PUVA therapy is not the most convenient therapeutic option for LP patients because they need to travel to the phototherapy center for each treatment session. More importantly, PUVA increases the

TABLE 16-7—Aloe Vera for Mucosal LP

Study	Design	No. of Patients	Comparators	Therapy Duration	Efficacy Outcomes*	Safety Results	Post Treatment Follow-up Duration	Notes
Choonhakarn 2008 ⁶⁰	Randomized, double-blind, placebo-controlled, parallel, single center trial	27 vs. 27	Aloe vera gel vs. placebo gel twice daily	8 weeks	Clinical response (Thong-prasom score), 0-10 VAS pain score	2/27 (7.4%, mild itching) vs. 0/27 (0%), p>0.05	No follow-ups	OLP (2 had CLP too)
Rajar 2008 ⁶²	Randomized, double-blind, placebo-controlled, parallel single center trial	17 vs. 17	Aloe vera gel vs. placebo gel twice daily	8 weeks	Clinical response (Thongprason score)	No side effects	No follow-ups	Vulvar LP (5 had CLP too) Control gel did not contain the baseline ingredients of the active gel.
Salazar-Sánchez 2010 ⁶¹	Randomized, double-blind, placebo-controlled, parallel single center trial	32 vs. 32	Aloe vera gel vs. placebo gel twice daily	12 weeks	Clinical response (Thongprason score), Hospital Anxiety-Depression (HAD) scale., OHIP-49, 0-10 VAS pain complete remission	No side effects	No follow-ups	Symptomatic OLP

*Efficacy results have been presented in Figure 16-7.

CLP, cutaneous lichen planus; HAD, ; QID, four times a day; OLP, oral lichen planus; VAS, visual analogue system; OHIP, oral health impact profile.

TABLE 16-8—Other Treatments for Mucosal LP

Study	Design	No. of patients*	Comparators	Therapy Duration	Efficacy results	Safety results	Post Treatment Follow-up Duration	Notes
Lodi 2007 ⁸⁸	Randomized, double-blind, active-controlled, single center trial	18 vs. 17 (17 vs. 17)	Miconazole 2% gel once daily plus clobetasol propionate 0.05% gel twice daily vs. clobetasol propionate 0.05% gel twice daily and placebo once daily	6 weeks	0-10 VAS symptoms 2.2 ± 1.8 vs. 2.4 ± 2.2; extension of lesions 19.3 ± 12.1 vs. 13.3 ± 11.9, p>0.05 for both	Candidosis: 0/15 (0%) vs. 5/10 (50%), p= 0.04	No	Symptomatic OLP; No follow-up was performed.
Lundquist 1995 ⁶³	Randomized within patient, open label, single center trial	18 left vs. 18 right lesions (16 vs. 16)	PUVa vs. methoxsalen 0.6 mg/kg without UVA as control for 12 sessions	22-33 days	Clinical improvement: 13/16 (81.3%) vs. 6/16 (37.5%), p<0.05	Indistinguishable due to within patient nature of the study (nausea, photosensitivity, paresthesia, headache)	1 year	Erosive/ulcerative OLP; Left and right (within patient) design would limit the interpretation of the results. ⁸⁹
Sardella 1998 ⁶⁹	Randomized, active controlled, single center trial	11 vs. 14	Mesalazine 5% gel vs. clobetasol propionate 0.05% ointment twice daily	4 weeks	Symptom improvement: 10/11 (90.9%) vs. 11/14 (78.5%), p>0.05	No side effects	No	Atrophic/erosive OLP (2 patients with CLP too)
Jajarm 2011 ⁷²	Randomized, open label, active controlled, single center trial	15 vs. 15 (11 vs. 13)	Low intensity laser therapy once every third day vs. Dexamethasone mouth wash plus 30 mystatin drops four times a day	4 weeks	Clinical cure: 2/11 (18.1%) vs. 3/13 (23.0%), p>0.05; Clinical improvement: 10/11 (90.9%) vs. 11/13 (84.6%); Relapse: 50% vs. 60%, p>0.05	0/11 (0%) vs. not reported	12 months	Atrophic/erosive OLP
Chainani-Wu, 2007 ⁶⁸	Randomized, placebo-controlled, double-blind, single center trial	16 vs. 17 (12 vs. 16)	2000 mg of curcuminoids plus 60 mg prednisone per day vs. placebo plus 60 mg prednisone per day	1 week for prednisone and 7 weeks for curcuminoids	Change in symptoms and signs from baseline: no significant difference between groups	Candidiasis: 1/16 (6.3%) vs. 0/16 (0%, p>0.05); No significant difference in side effects (insomnia, mood changes, and bloating)	No	Atrophic/ erosive OLP; Well explained randomization concealment method

(Continued)

TABLE 116-8—Calcineurin Inhibitors for Mucosal LP (Continued)

Study	Design	No. of patients*	Comparators	Therapy Duration	Efficacy results	Safety results	Post Treatment Follow-up Duration	Notes
Xiong 2009 ⁶⁵	Randomized active controlled, assessor-blind, single center trial	31 vs. 25 (27 vs. 22)	Intralesional injection of 0.5 ml BCG-PSN every other day vs. intralesional injection of 10 mg triamcinolone acetonide every week	2 weeks	Clinical cure: 27/31 (87.0%) vs. 22/25 (88%); Erosive area: 27.86±27.97 vs. 25.68±34.65; VAS score: 2.45±1.64 vs. 2.40±1.38, p>0.05 for all	3/31 (9.7%) vs. 2/25 (8.0%), p>0.05	3 months	Erosive LP, Sufficient follow-up duration
Wu 2010 ⁶⁶	Randomized, active-controlled, double-blind, single center trial	37 vs. 32 (18 vs. 17)	Thalidomide 1% paste vs. dexamethasone 0.043% paste, three times daily	1+3 weeks	0-10 VAS pain score: 2.77±2.00 vs. 2.88±1.45, p>0.05; Erosion free: 18/33 (54.5%) vs. 17/30 (56.6%), p>0.05	Burning sensation: 2/37 (5.4%) vs. 2/32 (6.3%), p>0.05	3 months for recurrence, 12 months for adverse events	Erosive OLP
Agha-Hosseini 2009 ⁶⁶	Randomized double-blind, placebo controlled, multicenter trial	20 vs. 17	Single dose of Purslane (235 mg) vs. placebo	1 day	Clinical improvement: 17/20 (85.0%) vs. 3/17 (17.6%), p<0.05; Symptom relief 20/20 (100%) vs. 12/17 (70.5%), p<0.05	No side effects	6 months	Mucosal LP (mainly OLP), long term follow-up
Nolan 2009 ⁷⁵	Randomized, double-blind, placebo controlled, single center trial	62 vs. 62 (113)	Hyaluronic acid 0.2% gel vs. placebo 4-5 times daily	4 weeks	Pain VAS, p>0.05; erosive / ulcerated area: -3.1±0.7 vs. -2±0.7, p<0.05	No side effects	No	Atrophic/erosive OLP
Mousavi 2009 ⁷⁴	Randomized investigator-blind, placebo controlled, single center trial	15 vs. 15	Single dose of Ignatia vs. placebo every month	4 months	Lesion size: 2.2 vs. 4.3, p<0.05; VAS pain score: 1.3 vs. 4, p<0.05	No side effects	No	Atrophic/erosive OLP; No standard deviation was reported for all mean values.
Lin 2005 ⁷³	Randomized open label, active controlled, single center trial	47 vs. 47	Tripterygium hypoglaicum tablet (2.7 gr/day) vs. Tripterygium glycosides tablet (1-1.5mg/kg/day)	3 months	Erosion improvement: 41/47 (87.2%) vs. 29/47 (61.7%), p<0.05; For ulcerative subtype: 18/21 (85.7%) vs. 11/21 (52.3%), p<0.05	Menstrual disturbance: 6/24 (25%) vs. 0/22 (0%), p<0.05; Leukocytopenia: 1/47 (2.1%) vs. 0/47 (0.0%), p>0.05	No	Erosive OLP; The study lacks a proper control group (placebo or an established therapy for OLP)

* The numbers in the parenthesis denote the number of patients per group who finished the study.
BCG-PSN, Polysaccharide nucleic acid fraction of bacillus Calmette-Guerin; CLP, cutaneous lichen planus; OLP, oral lichen planus; PUVA, psoralen plus ultraviolet A; VAS, visual analogue system.

risk of squamous cell carcinoma and this can magnify OLP's malignant potential. Because of PUVA's side effects and aforementioned concerns, it should be reserved for generalized LP or refractory erosive OLP cases. Furthermore, narrowband UVB phototherapy can be considered as an alternative.

Thalidomide

Thalidomide, or alpha-Phthalimido Glutarimide, is a racemic glutamic acid derivative synthesized in Germany in 1956 by Kunz, Keller, and Muckter. Topical thalidomide has been used for aphthous stomatitis, graft versus host disease, and chronic discoid lupus erythematosus.

EFFICACY: Wu et al. have demonstrated comparable efficacy results of thalidomide 1% paste and dexamethasone 0.043% paste for erosive OLP.⁶⁴

SAFETY: It was a 1-4 weeks thalidomide treatment period and the investigators observed no major side effects. The frequency of burning sensation was the same as dexamethasone group.⁶⁴

LIMITATIONS AND COMMENTS: Oral thalidomide has several serious adverse effects (e.g., teratogenicity, neurotoxicity, and venous thromboembolic events). Moreover, there is no long-term follow-up study and/or phase 4 clinical trials for topical thalidomide to prove its efficacy and safety. Thus, topical thalidomide 1% should be reserved as a second or third line short-term medication.

Polysaccharide nucleic acid fraction of bacillus Calmette-Guerin (BCG-PSN)

Bacillus Calmette-Guerin polysaccharide nucleic acid (BCG-PSN), the third-generation BCG extract with various immunologic active materials including polysaccharide and nucleic acid, has the ability to regulate the subsets of T cells (CD4 and CD8 cells) and subtypes of helper T cells (Th1 and Th2).⁶⁵

EFFICACY: In one trial, BCG-PSN was compared with triamcinolone intralesionally and 87% versus 88% of patients had clinical cure, respectively.⁶⁵

SAFETY: Burning sensation and swelling occurred in 9.7% of patients in the BCG-PSN group versus 8% of patients in triamcinolone group.⁶⁵

LIMITATIONS AND COMMENTS: Generally, intralesional injections can be used for non-healing hypertrophic or erosive lesions. BCG-PSN can be considered in this regard.

Purslane

Portulaca oleracea (Purslane) is an annual succulent in the family Portulacaceae. It contains several biologically

active compounds including omega-3 fatty acids, minerals, β-carotene, melatonin and vitamins A, C and E.⁶⁶

EFFICACY: One randomized placebo-controlled study, proved a dramatic effect of single dose Purslane (235 mg) even after 6 months.⁶⁶

SAFETY: No side effects were reported. Purslane should be used with caution in patients with kidney stones.⁶⁶

LIMITATIONS AND COMMENTS: More trials on this remedy for OLP would be of interest and may support its use as a second line therapy.

Curcuminoid

Curcuminoid is a curcumin and/or a derivative of curcumin with different chemical groups that are formed to increase solubility of curcumins and make them suitable for drug formulation.⁶⁷

EFFICACY: Chainani-Wu et al. showed no difference between curcuminoid plus oral prednisone versus oral prednisone only.⁶⁸

SAFETY: No curcuminoid-related side effect was observed.⁶⁸

LIMITATIONS & COMMENTS: Such a design to investigate the additive effects of curcuminoid to 60 mg oral prednisone may underestimate the efficacy of curcuminoid. Curcuminoids cannot be recommended for mucosal LP.

Miconazole

Miconazole, an antifungal agent, is mainly used for skin infections such as athlete's foot, tinea cruris and vaginal yeast infections.

EFFICACY: Miconazole 2% gel once daily plus clobetasol propionate 0.05% twice daily treatment had a similar clinical response comparable with clobetasol propionate 0.05% only treatment.⁸⁸

SAFETY: Oral candidiasis occurred in 0% versus 50% of patients with or without miconazole treatment, respectively.⁸⁸

LIMITATIONS AND COMMENTS: Miconazole is recommended to avoid candidiasis in mucosal LP but is not recommended as a therapeutic agent for LP lesions.

Mesalazine

Mesalazine or 5-aminosalicylic acid (5-ASA), is an anti-inflammatory drug used to treat inflammatory bowel diseases such as ulcerative colitis and mild-to-moderate

Crohn's disease. Mesalazine is a bowel-specific aminosalicylate drug that acts locally in the gut and has its predominant actions there, thereby having few systemic side effects.⁶⁷ It is also the active component of sulfasalazine.

EFFICACY: One RCT compared mesalazine 5% gel with clobetasol propionate 0.05% and found similar efficacy.⁶⁹

SAFETY: Sardella et. al. noted no side effect with mesalazine.⁶⁹

LIMITATIONS AND COMMENTS: As other studies reported that gastric side effects occurred after using higher concentrations of mesalazine gel or foam,^{70,71} long-term follow-up studies are needed to ascertain its safety for mucosal LP.

Low-level laser therapy

Low-level laser therapy (LLLT) is a controversial modality treatment that uses low-level lasers or light-emitting diodes to alter cellular function.

EFFICACY: One randomized trial found comparable clinical improvement rate for low level diode laser and dexamethasone mouth rinse for atrophic/erosive OLP.⁷²

SAFETY: Low-level laser has no major side effect.⁷²

LIMITATIONS & COMMENTS: Historically, this modality has been debatable and controversial for different applications. More evidence is needed for mucosal LP.

Tripterygium

“Tripterygium Hypoglaucum” tablet is a purified product of the effective ingredients of decorticated radix tripterygium hypoglaucum, which is extracted in boiling water and precipitated by alcohol. This purification technique is different from that of making “tripterygium glycosides”, and can reduce the toxic ingredients in the preparation process. The good thing about both traditional Chinese herbs is that they do not act like glucocorticoids and therefore can be used as alternatives to corticosteroids in different diseases or in conditions like facial addiction to topical corticosteroid.⁷³

EFFICACY: One randomized open label trial compared these two herbs with each other. It seems that tripterygium glycosides is significantly more effective than tripterygium hypoglaucum in healing the erosive-ulcerative lesions whereas tripterygium hypoglaucum has a better safety profile.⁷³

SAFETY: Tripterygium glycosides can cause menstrual disturbances (25%) and leukocytopenia (2%). Tripterygium hypoglaucum can cause fewer side effects.⁷³

LIMITATIONS AND COMMENTS: There was no placebo control or a topical or oral corticosteroid control in this study. Hence, none of them may be recommended for mucosal LP.

Ignatia

Ignatia is a homeopathic remedy that is derived from the bean of a small tree that is native to the Philippine Islands and China.

EFFICACY: There is only one placebo-controlled trial for ignatia. It reported a significant effect of ignatia on lesion size and pain score.⁷⁴

SAFETY: No side effects were reported for ignatia.⁷⁴

LIMITATIONS AND COMMENTS: The presentation of the data is not sufficient to conclude a definitive effect.

Hyaluronic acid

Hyaluronic acid (HA) is one of the chief components of the extracellular matrix. It has a relatively short half-life and that is why several efforts have been made to optimize its stability. It has been approved as a drug for corneal and epithelial wound healing.

EFFICACY: One double blind randomized trial compared (HA) 0.2% with placebo and found that HA 0.2% can be partially helpful, especially in short term periods (less than 4 hours), in relieving the symptoms. It also had no effect on erosion size after 28 days when compared with placebo. Additionally, 0.2% HA had no effect on the extent and severity of the OLP as described by Thongprasom's criteria.⁷⁵

What We Know: CLP

- The high quality evidence is extremely lacking for CLP. There is an emergent need for conducting randomized-controlled trials.
- Primary treatment options for mild to moderate CLP would be topical corticosteroids and immunomodulators but there is no strong evidence to support them. Only one study supports the additive effects of oral prednisone to topical hydrocortisone-17-butyrate.
- For generalized LP or resistant cases, systemic corticosteroids, immunosuppressive drugs, PUVA, or biologics can be administered. However, there is no supporting evidence for this.
- Life-long clinical follow-up is fundamental.

What We Know: Mucosal LP

- Currently, the main therapeutic goal in the treatment of mucosal LP is not immediate complete cure. The main focus should be on relieving pain and discomfort in the mouth during talking, eating, drinking, and genitalia during intercourse.
- Although topical corticosteroids are considered as the mainstay of mucosal LP therapy, only two of them have been proven to be more beneficial than placebo.
- Calcineurin inhibitors can be considered as second line therapy. Tacrolimus is more effective than clobetasol and triamcinolone in two RCTs. Cyclosporine and pimecrolimus are at least as effective as topical corticosteroids. Relapse can occur in many patients after tacrolimus and pimecrolimus treatment.
- Topical retinoids are more effective than placebo.
- Aloe vera may be beneficial in the treatment of mucosal LP. The only RCT that assessed vulvovaginal LP patients found aloe vera useful.
- Life-long clinical follow-up is fundamental.

SAFETY: It is a relatively safe therapeutic option at a 0.2% concentration.

LIMITATIONS & COMMENTS: The efficacy of HA is under question. It may only be considered as a supportive component of a combination therapy. It has to be applied in a frequent fashion to maintain its efficacy (e.g. 6 times a day). It warrants further investigation.

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ADDITIONAL SOURCES

Ongoing or unpublished Studies:
<http://clinicaltrials.gov/ct2/show/NCT00568581>
<http://clinicaltrials.gov/ct2/show/NCT00135733>
<http://clinicaltrials.gov/ct2/show/NCT00102557>
<http://clinicaltrials.gov/ct2/show/NCT00111072>

Treatment of Pemphigus

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BACKGROUND

Pemphigus is a group of rare autoimmune bullous diseases caused by the dissociation of keratinocytes, leading to the formation of bullae and erosions. It is a chronic, potentially life-threatening condition characterized by widespread blistering of the skin and mucous membranes.

EPIDEMIOLOGY

The incidence of pemphigus has been estimated between 1 to 10 new cases per million people per year¹ with some genetic variance observed. For instance, the incidence is higher in Japanese, Indian, Arabic, and Ashkenazi Jewish populations compared to that observed in North America or Western Europe with HLA class II alleles potentially involved in the pathogenesis of pemphigus.² Sex distribution is equal across men and women, and the disease most commonly starts in adulthood.

ETIOLOGY

Pemphigus is an organ-specific autoimmune disease. The exact pathophysiologic mechanisms underlying the derangements in immunity have yet to be elucidated, however, the disease is characterized by the production of autoantibodies directed against desmogleins, transmembrane proteins located on desmosomes responsible for cell-to-cell adhesion, leading to acantholysis.

The clinical phenotype of pemphigus depends on the tissue distribution of the particular desmoglein that autoantibodies are directed against. Desmoglein 1 is distributed in the granular epidermal layer and limited to the skin, while desmoglein 3 is located in the basal epidermis and found in both the skin and mucous membranes. The clinical picture depends on which desmogleins are targeted in the autoimmune process.³ Rarely, additional target antigens have been identified in pemphigus, including desmocollins, acetylcholine receptors and other autoantigens.⁴ Triggering of apoptosis pathways is also important in pemphigus, with involvement of downstream phosphorylation signalling

pathways.⁵ Besides the humoral pathway generating autoantibodies, T-cell pathways are also involved in the epitopes that generate an immune response with derangements present in the normal immunologic regulatory pathways.⁶

Pemphigus vulgaris (PV) is the most common type of pemphigus, characterized by the presence of autoantibodies against desmoglein 3, which is why the oral mucous membrane is often involved initially. Involvement of desmoglein 1 and desmocollins via epitope spreading is also possible. Patients typically present with nonhealing oral erosions which progress to involve the skin after a period of months. Autoantibodies are directed against desmoglein 1 in pemphigus foliaceus (PF), so patients present with blistering and erosions limited to the skin with the mucous membranes spared.

Other forms of pemphigus exist, including paraneoplastic pemphigus, drug-induced pemphigus, pemphigus vegetans, pemphigus erythematosus and pemphigus herpetiformis. This review will be limited to the most common types of pemphigus – PV and PF.

DIAGNOSIS

Diagnosis of pemphigus is based on a combination of clinical features, histopathologic review and immunofluorescence (IF) studies. The clinical features of pemphigus include flaccid blisters, oral ulcers, and superficial erosions. Light microscopy of lesional biopsies demonstrates intraepidermal acantholysis, vesicle formation, and the upward growth of papillae lined by a single layer of epidermal cells. Confirmation of the diagnosis necessitates the use of immunofluorescence, because of the difficulty of differentiating pemphigus from other bullous diseases. Direct immunofluorescence of perilesional biopsies reveals intercellular epidermal deposits of IgG, with or without C3, and indirect immunofluorescence on monkey esophagus reveals antibodies to keratinocyte surface antigen in PV. Indirect IF can be done in dilutions to give an idea about the degree of activity of the pemphigus. Enzyme-linked immunosorbent assay (ELISA) measures the titration of

specific desmoglein 1 or 3 antibodies circulating in the serum. It is more sensitive than titers done on indirect IF. In some research laboratories, immunoblotting studies are available, which allow identification of particular antigens, and may prove useful for diagnosis and prognosis.

PROGNOSIS

Pemphigus is a potentially life-threatening condition with chronic blistering, capable of causing fluid depletion, secondary infection or sepsis, and in rare cases, death. Prior to the age of corticosteroids, mortality was approximately 70% as a result of sepsis.⁷ With the advent of corticosteroids, mortality is now 6%, with most deaths attributable to side-effects of steroid therapy.⁸ The literature provides a limited understanding of the prognostic factors in pemphigus, but PV is reported to have a worse prognosis than PF⁹ and in the setting of PV, disease limited to the mucosa is associated with a better prognosis than disease with combined mucocutaneous involvement.¹⁰

MANAGEMENT

The aim of management in pemphigus is to induce and maintain remission, which is defined as “the absence of new or established lesions while the patient is off all systemic therapy for at least 2 months”,¹¹ while minimizing the adverse effects of treatment. In stating this, it is important not to overtreat the patient; the presence of a few transient blisters means that the treatment is not too strong, as that is the source of most morbidity in the long-term management of pemphigus.

At present, treatment regimes are more ‘eminence-based’ than evidence based, and there is no consensus amongst international experts regarding the treatment of pemphigus,¹² although some countries have their own national guidelines.¹³ This is largely because of the fact that there have been less than a dozen well-designed, double-blind, randomized-controlled trials (RCTs) reviewing the treatment of the disease.¹⁴ The numbers of patients included in most of these RCTs was too low in most cases to have sufficient power to determine a statistically significant difference. Pemphigus is a rare condition in most countries, making patient recruitment a challenge, and therefore most clinical trials in AIBD tend to involve small cohorts of patients. Most studies are open and uncontrolled with patients of assorted disease severities often treated concomitantly with a number of therapies, making it difficult to evaluate the benefits of a given treatment.

There has also been a lack of suitable endpoints in clinical studies to measure the outcomes of intervention, although international consensus definitions of outcome measures for pemphigus have recently been developed.¹¹ Objective instruments, which quantify disease activity, such as the Autoimmune Bullous Skin Disease Intensity Score (ABSIS),¹⁵ and the Pemphigus Disease Activity

Index (PDAI),¹⁶ may provide a suitable endpoint in clinical studies, as well as quality-of-life instruments, which have become increasingly employed in the field of dermatology to evaluate disease status.¹⁷

Outcomes that have been previously used to assess disease control include effectiveness in preventing new vesicle formation, the healing of pre-existing lesions, the time taken to achieve disease control, and antibody titers. Long-term outcomes have included the proportion of patients able to discontinue treatment and the proportion of patients that relapse. Cumulative steroid dose has also been utilized as an outcome in the literature as a proxy for steroid-induced adverse events, as this is the major cause of mortality in pemphigus. Further research is warranted in developing standardized outcome measures to enable effective, evidence-based comparisons of the wide range of interventions employed in the management of pemphigus.

CORTICOSTEROIDS

Corticosteroid dosing

Systemic glucocorticoids are the cornerstone of treatment. The advent of corticosteroids in the 1950s was accompanied by a 45% reduction in mortality,⁷ but the long-term, high-dose courses of systemic corticosteroids often used to control pemphigus are associated with significant sequelae.¹⁸ There is no standardized approach to the administration of corticosteroids in pemphigus, although continuous oral administration is the most common. It has been put forward that corticosteroids should be initiated at a high enough dose to control disease and tapered thereafter once the majority of lesions have healed. The optimal dosing strategy has yet to be determined and it has also been argued that high dose, pulsed therapy may achieve faster disease control and offer the patient a reduced cumulative glucocorticoid dose.¹⁹

There has only been one RCT investigating steroid dosing regimens in pemphigus.²⁰ In this study, 22 newly diagnosed patients with greater than 50% of body surface area affected were randomized to low-dose (45-60 mg) (n=11) or high-dose (120-150 mg) (n=11) prednisolone and followed for 5 years. All patients were treated until remission, after which their steroid dose was tapered to 20 mg. From this point, either adjuvant cyclophosphamide 100 mg or methotrexate 15 mg weekly was randomly introduced and the prednisolone dose decreased to 2.5 mg per month. All patients had resolution of blister formation and were seronegative for autoantibodies at 3 months. There was no significant difference in the duration of treatment needed to achieve initial remission, the number of relapses or the timeframe to relapse, or the incidence of complications between the two groups, indicating that there was no short-term or long-term advantage to a high-dose regimen. However, the numbers in this small study were insufficient to perform adequate statistical analysis.

Fernandes and Perez report a retrospective, nonrandomized controlled trial involving 71 patients (41 PV/30 PF).²¹ Patients were assigned to cohorts receiving prednisone 1 mg/kg/day ($n=34$) or 2 mg/kg/day ($n=37$) based on clinical severity at presentation and followed for 5 years. Both cohorts were kept on prednisone for 4-6 weeks until remission, after which the prednisone dose was tapered. No statistical difference was observed between cohorts in terms of response to treatment, however, there was a significantly higher frequency of adverse events, particularly infection, in the 2 mg/kg/day cohort. Despite the retrospective, nonrandomized nature of the study, the results indicate that higher doses of corticosteroid are no more effective than lower doses, and are associated with higher rates of complications.

Overall, the limited evidence indicates that lower steroid dose regimens (at around 1 mg/kg/day) may be sufficient for initial control of pemphigus in most patients and may have decreased associated morbidity. At our institution, we commence therapy with 1 mg/kg/day of oral prednisone for pemphigus. Once the patient has reached the end of the consolidation phase, we begin to taper the prednisone slowly. At high doses, we give divided doses of steroids to reduce hyperglycaemic effects. We add a steroid-sparing drug (see below) and follow the steroid taper used by Werth's group from 40 mg to zero over about 4 months. Patients are tapered by 5 mg a week to 20 mg a week, then by 2.5 mg a week to 10 mg a week, then by 1 mg a week to 3 mg/week. If an 8:00 a.m. cortisol is normal at that point, then prednisone taper by 1 mg a week is continued. Using this combination and duration of treatments, most of our patients have been able to go into clinical remission on low dose steroid-sparing agents.

Pulse Corticosteroid Therapy

Pulse therapy refers to discontinuous intravenous infusion of high-dose glucocorticoids in a short burst. It is based on the rationale that the steroid pulses may cause rapid control of disease and decrease the need for long-term steroid use, thereby reducing the complications of long-term usage.²²

The only RCT evaluating the utility of pulse therapy in pemphigus had only 20 patients with newly diagnosed PV, or new disease activity randomized to oral dexamethasone 300 mg ($n=11$) or placebo ($n=9$) pulses three days per month.²³ Both treatment cohorts also received prednisolone 80 mg/day tapered over 19 weeks and azathioprine 3 mg/kg/day, with pulse therapy continued until the prednisolone dose reached zero. Patients were followed for 1 year. There was no significant difference between cohorts in the time to remission, duration or remission or relapse rate. The cumulative steroid dose was higher in the dexamethasone cohort as was the rate of adverse effects. No benefit was able to be demonstrated in the use of oral dexamethasone pulse therapy in addition to conventional treatment. With

only 20 patients in the study, we cannot conclude from this that there would be no benefit from oral dexamethasone pulse therapy.

Femiano et al. have reported an open, nonrandomized, controlled trial of 20 PV patients with participants receiving either a 125 mg/day tapering schedule of prednisone ($n=10$) or a 50 mg/day tapering schedule of prednisone plus i.v. bethamethasone 20 mg/day.²⁴ In this study, the cohort receiving the pulse therapy was found to have minimal differences in resolution of symptoms and oral lesions (30 vs. 25 days).

In addition, there have been a number of case series reporting the use of pulse steroids.

In 1995, Chryssomallis et al. first reported 8 patients with severe or recalcitrant treated with 6-10 pulses of i.v. methylprednisolone 8-10 mg/kg on alternate days plus oral prednisone 0.4-1 mg/kg/day and either azathioprine or cyclophosphamide.²⁵ All patients achieved disease control, healing at least 50% of lesions, but none could discontinue therapy, and one patient died of a cardiac arrest. Werth et al. reported nine PV patients who did not initially respond to prednisone, receiving i.v. methylprednisolone 250-1000 mg/day for 1-5 days in addition to adjunctive treatment.¹⁹ During the pulse therapy, six of nine patients improved and four of nine were able to discontinue treatment for an average of 2 years. A steroid-sparing effect was observed compared to a historic control group. Mignogna et al. reported 12 pemphigus patients treated with i.v. methylprednisolone 30 mg/kg for 3-5 days on cycles of 21 days.²⁶ In all patients, remission was observed by the third cycle, however nine of 12 cases relapsed during the 6-month follow-up and every patient had some adverse effect.

Toth et al. reported a retrospective series of 14 patients treated with 60 mg/kg oral prednisone and 200-300 mg pulse dexamethasone for 3 days monthly.²² Remission was established in five of 14 patients after one pulse treatment and in a further two out of 14 patients after 2 pulses, and was sustained for 2-15 months thereafter. Minor adverse effects were observed in approximately 60% of cases.

While these early case series of pulsed corticosteroids appeared promising, evidence from the more recent controlled trials have not demonstrated that pulsed steroids confer any clear additional benefit and that they may be associated with a higher incidence of side-effects. Notably, the case series described had patient cohorts with predominantly severe or recalcitrant disease while patients in the two studies were predominantly newly diagnosed, which may account for some of the observed dichotomy.

ADJUVANT IMMUNOSUPPRESSIVE THERAPY

Adjvant steroid-sparing therapies have been employed in the management of pemphigus, with the belief that they not only reduce the cumulative glucocorticoid dose but increase the efficacy of treatment. Common adjvant

therapies utilised include azathioprine, mycophenolate mofetil, cyclophosphamide and cyclosporine. These agents typically require 4-12 weeks to demonstrate any therapeutic effect, so their use is essentially in maintaining remission and allowing steroid taper, rather than inducing remission.

A recent RCT by Chams-Devatchi et al. of 120 newly diagnosed PV patients compared prednisone monotherapy (n=30) with prednisone plus adjuvant azathioprine (n=30), mycophenolate mofetil (n=30) or intravenous cyclophosphamide pulse therapy (n=30).²⁷ All four regimens induced complete remission in 70-80% patients with no statistically significant difference observed between them in terms of remission or side-effects. However, the mean cumulative steroid dose in the prednisone cohort was significantly higher than the mean in the adjuvant cohorts ($p=0.047$), suggesting a steroid-sparing role of adjuvant therapy. The authors proposed that azathioprine was the most efficacious steroid-sparing agent, followed by cyclophosphamide, then mycophenolate mofetil based on the mean cumulative steroid dose between cohorts.

A retrospective case series of 101 patients with moderate to severe PV by Olszewska et al. also compared prednisone monotherapy with adjuvant azathioprine, cyclosporine, and cyclophosphamide.²⁸ Patients were treated with oral prednisone 1.1-1.5 mg/kg/day (n=20) or prednisone combined with azathioprine 100 mg (n=16), cyclosporine 2.5-3 mg/kg (n=14) or cyclophosphamide 100 mg 1.1-1.5 mg/kg (n=51). Clinical remission was achieved significantly faster in the cyclophosphamide cohort, compared to other patients, and resolution of PV antibodies was faster in the cyclophosphamide cohort compared to the prednisone cohort. Disease activity was significantly lower in the cyclophosphamide cohort after 3 months of therapy, and significantly higher in the cyclosporine cohort at 12 months compared to the other participants. The safety profile was similar across cohorts. In this study, the authors proposed that cyclophosphamide should be the drug of choice in PV.

The majority of evidence for the use of adjuvant therapy has been based on case series as there have been limited RCTs published on the topic.

Azathioprine

The use of combined prednisone and azathioprine is commonly employed regimen in pemphigus and is usually well-tolerated.

In Chams-Devatchi's RCT, disease control was achieved in 80% of patients in the azathioprine cohort after 1 year, and the cumulative steroid dose was significantly lower than that of the prednisone monotherapy and prednisone plus mycophenolate mofetil cohorts.²⁷ However, another randomized trial comparing azathioprine with mycophenolate mofetil in 40 pemphigus patients failed to demonstrate any significant difference between the two therapies in terms of remission, relapse rates, cumulative

steroid dose or adverse effects according to the author's protocol.²⁹

Akhtar and Hasan reported a nonrandomized-controlled trial in 72 patients comparing prednisolone (n=40), prednisolone plus azathioprine (n=15) and betamethasone-cyclophosphamide pulse therapy (n=17).³⁰ The regimen consisted of prednisolone 30-120 mg/day given on a tapering schedule alone or in combination with azathioprine 100-150 mg/day. Treatment with azathioprine was more effective in terms of the proportion of patients achieving disease control, and the frequency of relapses and incidence of complications was lower in the azathioprine group.

The largest case series on azathioprine was a prospective, long-term study of 37 patients treated with methylprednisolone 80-200 mg plus azathioprine 2-3 mg/kg/day.³¹ In the follow-up ranging from 4-16 years, "complete clinical remission" was reported in all patients evaluated, although 66% of patients experienced relapses. At the time of evaluation, 24/37 patients were disease free, five of 37 had improved but were not disease free, and two of 37 had failed on this regimen.

Azathioprine has been shown to have a steroid-sparing role and it is put forward that it is therefore likely to reduce steroid-related complications. Its role in disease control has not been satisfactorily established, but based on the limited evidence in the literature it appears adjunctive azathioprine is beneficial. On the basis of this evidence and our experience, we check thiopurine methyl transferase levels and if not very low, we commence azathioprine early at 2.5 mg/kg/day while the patient is on high doses of prednisone, and monitor bloods for safety every 2 weeks initially.

Mycophenolate mofetil

Mycophenolate mofetil is a relatively recent drug, which functions as an immunosuppressant by inhibiting the proliferation of lymphocytes.

In Chams-Devatchi's RCT, 70% of patients in the mycophenolate mofetil cohort achieved complete remission after 1 year and the cumulative steroid dose was significantly lower than that of the prednisone monotherapy cohort, indicating a potential steroid-sparing role for the agent.²⁷ A multicenter RCT randomised patients with mild or moderate PV to oral corticosteroid plus either mycophenolate mofetil (2 or 3 g/day) or placebo for 52 weeks.³² The primary outcome, response rate at 48 to 52 weeks was no different. However, there were several differences in the secondary outcome measures. Compared to the patients receiving placebo, patients on either dose of mycophenolate mofetil achieved a faster therapeutic response, maintained their response for longer and had a longer time to relapse. There was also an observed steroid sparing role of the immunomodulator, collectively indicating a more durable therapeutic outcome. Another randomized trial comparing azathioprine with mycophenolate mofetil demonstrated

that mycophenolate mofetil was more effective than azathioprine in achieving disease control, with complete healing reported in 20/21 (95%) of mycophenolate mofetil patients compared to 13/18 (72%) of azathioprine patients.²⁹

The largest case series, reported by Mimouni et al. reported 42 patients treated with mycophenolate mofetil 35-45 mg/kg/day in combination with prednisone 1 mg/kg/day.³³ The patients included had either relapsed during prednisone taper or had experienced adverse effects on azathioprine. Remission was achieved in 27/42 patients with a steroid dose of less than 0.15 mg/kg/day after a median of 9 months. The therapy was well-tolerated with 77% of patients having no adverse effects.

Powell et al. reported 17 patients with severe, recalcitrant pemphigus treated with mycophenolate mofetil 2.5 g/day and prednisone 15-60 mg/day.³⁴ Within 3 months, eight of 17 patients had clinically inactive disease and four of 17 improved with ongoing lesion. Two patients were clinical failures, one patient withdrew because of poor disease control, and two withdrew after reporting paresthesias.

Chams-Davatchi described 10 patients with severe pemphigus vulgaris refractory to azathioprine, and multiple other adjuvants.³⁵ Patients were treated with 2000 mg/day mycophenolate mofetil for 6 months and a tapering schedule of prednisone. Nine of 10 patients had clinical resolution of lesions after a mean of 3.4 months and a steroid sparing effect was observed. Two patients relapsed during the trial and one patient failed to respond. Five patients relapsed within 3 weeks of discontinuing mycophenolate, indicating that courses of longer than 6 months are required for sustained remission.

Overall, the evidence suggests that mycophenolate mofetil serves a steroid-sparing role and there is some evidence to suggest it may be superior to azathioprine in terms of disease control. Case series report the successful use of adjuvant mycophenolate mofetil in patients with refractory disease with minimal side-effects observed, however treatment failures are also reported in a small proportion of these patients. As mycophenolate mofetil is significantly more expensive than azathioprine and the steroid-sparing difference is minimal in these studies, it is our practice to start with azathioprine and if there are side effects or lack of efficacy, to switch to mycophenolate mofetil later. If the patient has a contraindication to azathioprine, then we commence mycophenolate mofetil instead.

Cyclophosphamide

Cyclophosphamide is an alkylating agent used as an adjuvant in pemphigus. While there are case reports of successful cyclophosphamide therapy, there are also series, which suggest it has limited utility as a monotherapy³⁶ and the substantive evidence of its benefit is in combination with corticosteroids.

An RCT by Chrysomallis et al. compared prednisone monotherapy and the use of adjuvant cyclophosphamide

or cyclosporine.³⁷ Patients with newly diagnosed mucosal PV were randomized to either prednisone 40 mg (n=10), or prednisone with cyclophosphamide 100 mg/day (n=10) or cyclosporine 5 mg/kg/day (n=10) and followed for 5 years. There was no significant difference between the three cohorts in terms of time to remission or relapse rates. Combination therapy cohorts were reported to have a higher incidence of adverse events, although these were mild.

Cummins et al. reported 23 patients (20PV, 3PF) treated with oral cyclophosphamide 2-2.5 mg/kg and prednisone 1 mg/kg.³⁸ Five patients also received concomitant plasmapheresis. Seventeen of 23 patients achieved complete remission after a median of 8.5 months, although six relapsed subsequent to discontinuation of treatment after a median of 6 months. Adverse events occurred in at 14 of 23 patients including hematuria in five patients, infection, and one case of transitional cell carcinoma. Piampongsant reported 12 patients treated with prednisone 60-120 mg/day and cyclophosphamide 100 mg daily, on a tapering schedule.³⁹ Disease control was achieved in 9 of 12 patients on prednisone <15 mg/day plus cyclophosphamide 50 mg on alternate days or once a week, and 3 of 12 patients were able to stop treatment. No serious complications from cyclophosphamide therapy were reported. Fellner described five patients with newly diagnosed PV treated with oral cyclophosphamide 100-200 mg/day plus prednisone 200 mg/day.⁴⁰ All patients achieved disease control and four were able to discontinue medication.

A case series by Momeni et al. reported the use of oral cyclophosphamide with dexamethasone pulse therapy in 50 PV patients.⁴¹ Participants received oral cyclophosphamide 50 mg daily and i.v. dexamethasone 100 mg for 3 consecutive days repeated every 14 days, with i.v. cyclophosphamide 500 mg administered once at the onset of the study. At 10-year follow-up, 10 of 50 patients were free of lesions and 21 of 50 patients were in complete remission with the mean duration of remission of 5.7 years. One patient died from septicemia and Cushingoid features were observed in ten patients, but no serious side effects were otherwise reported.

In summary, adjuvant oral cyclophosphamide has been reported as effective in inducing remission in pemphigus. However, no studies have been performed demonstrating that the combination of steroid and cyclophosphamide is more efficacious than steroid monotherapy and the safety-profile of oral cyclophosphamide in the setting of pemphigus has not been fully elucidated.

Pulsed Cyclophosphamide

Pulsed intravenous cyclophosphamide has been reported to be more effective than oral cyclophosphamide in a number of autoimmune conditions, offering improved clinical outcomes and fewer side effects than daily oral therapy. It was thus anticipated that this modality may

also be effective in pemphigus. Three RCTs, one nonrandomized control trial and numerous case series have been reported, however, no studies to date compare oral and pulsed cyclophosphamide.

In Chams-Devatchi's RCT, 73.3% of patients in the pulse cyclophosphamide cohort achieved complete remission after 1 year and the cumulative steroid dose was significantly lower than that of the prednisone monotherapy cohort, indicating a potential steroid-sparing role of the modality.²⁷ It was not found to be superior to either azathioprine or mycophenolate mofetil in terms of disease control.

Rose et al. conducted an open RCT with 22 newly diagnosed pemphigus patients (16PV, 6PF) comparing combined methylprednisolone and azathioprine therapy with combined pulse i.v. dexamethasone and cyclophosphamide therapy.⁴² The methylprednisolone/azathioprine cohort were treated with methylprednisolone 2 mg/kg/day and azathioprine 2.0-2.5 mg/kg/day therapy (n=11) and the dexamethasone-cyclophosphamide cohort were treated with i.v. dexamethasone 100 mg on 3 consecutive days with cyclophosphamide 500 mg on day one, repeated every 2-4 weeks, in addition to oral cyclophosphamide 50 mg (n=11). At 24 months, remission was reported in five of 11 patients in the methylprednisolone/azathioprine cohort and one of 11 patients in the dexamethasone-cyclophosphamide cohort, with three of 11 patients in each cohort in remission having ceased therapy. Progression of disease was observed in one of 11 patients in the methylprednisolone/azathioprine cohort and six of 11 patients in the dexamethasone-cyclophosphamide cohort. No results of the study were statistically significant.

Another open, randomized trial compared dexamethasone-cyclophosphamide pulse and daily oral cyclophosphamide against cyclophosphamide pulse and daily oral prednisolone.⁴³ In Group A, fifteen patients received 100 mg of dexamethasone i.v. on three consecutive doses with a single dose of cyclophosphamide 500 mg i.v. repeated every 4 weeks as well as daily cyclophosphamide 50 mg (and oral prednisolone if disease activity was not controlled after two weeks). In Group B, thirteen patients received i.v. cyclophosphamide 15 mg/kg/day every 4 weeks along with daily oral prednisolone 1.5 mg/kg/day on a tapering regime. The total period of therapy was 12 months and at the conclusion of the study, there was a statistically significant difference in the time to initiation of a cutaneous response and the time to achieve remission in Group B. However, there was no difference in terms of time to initiation of a mucosal response and the re-epithelialization of lesions, nor any difference between cohorts in terms of autoantibody titers. In both groups the titers were significantly reduced from pretreatment levels. Relapse rates were >60% in both groups after cessation of therapy, indicating the need for maintenance therapy in this setting.

Akhtar and Hasan reported a nonrandomized, controlled trial comparing prednisolone (n=40), prednisolone

plus azathioprine (n=15), and pulsed betamethasone-cyclophosphamide pulse therapy (n=17), described previously in the discussion of azathioprine.³⁰ The regimen of the betamethasone-cyclophosphamide cohort consisted of pulsed i.v. betamethasone 100 mg/day for 3 days and cyclophosphamide 500 mg on day one, plus cyclophosphamide 50 mg orally daily. Twelve of 17 patients in the pulse cyclophosphamide cohort were considered treatment failures and required additional steroids. An increased susceptibility to infection was seen in the betamethasone-cyclophosphamide group compared to other arms and four of 17 patients died.

The results of these trials differ considerably from the numerous case series in the literature reporting similar protocols of pulse cyclophosphamide: pulse i.v. dexamethasone 100 mg/day for 3 days and cyclophosphamide 500 mg on day one, plus cyclophosphamide 50 mg orally daily. Pasricha et al. reported 300 pemphigus patients on cyclophosphamide pulse therapy for over 12 years. It was reported that 190/300 patients were 'disease free' on no medication, with remission continuing over 2 years in 123 patients.⁴⁴ Kaur & Kanwar reported 50 pemphigus patients treated with pulse therapy over 2 years.⁴⁵ Lesions were reported to resolve within days of commencing treatment and remission was induced in 28 of 50 patients. Kanwar et al. later reported on the long-term efficacy of this regimen in 36 patients (32PV, 4PF).⁴⁶ All patients were able to discontinue therapy and remain free of disease over a range of 0.5 to 12 years. Sacchidanand et al. reported 46 patients with advanced pemphigus (44PV, 2PF) of which 70% achieved clinical remission after three pulses.⁴⁷ Bhat et al. reported a case series of 26 patients (25 PV, 1PF) treated with an i.v. cyclophosphamide 15 mg/kg bolus monthly and daily prednisolone 1 mg/kg/day in which 82% of patients were free of all lesions after 12 months.⁴⁸

These case series offered predominantly positive outcomes, reporting rapid response to treatment and high rates of remission. However more recent controlled trials have not demonstrated any evidence to support the use of pulse cyclophosphamide therapy in pemphigus, although there is evidence that it serves a steroid-sparing role. It is our practice to only use pulse cyclophosphamide if less toxic treatments are ineffective.

Cyclosporin

Two RCTs and a number of case series have presented the use of cyclosporine in pemphigus.

Ioannides et al. reported an RCT of 33 patients with newly diagnosed pemphigus (29PV, 4PF).⁴⁹ Patients were randomized to treatment with prednisone 1 mg/kg (n=17) or prednisone and cyclosporine 5 mg/kg (n=16) and followed for 4-6 years. Multiple endpoints were employed to evaluate clinical response including the proportion of patients responding to therapy, the time required to achieve disease control, the proportion of patients who relapsed,

partial and complete remission rates, and cumulative steroid dose. No significant difference was observed between the two cohorts, although the incidence of adverse effects was higher in the cohort receiving cyclosporine. The RCT failed to demonstrate any advantage of adjuvant cyclosporine in the management of pemphigus. Similarly, the RCT of Chrysomallis et al. described previously in the discussion of cyclophosphamide failed to demonstrate any benefit of adjuvant cyclosporine in the time to achieve disease control, the proportion of patients responding, or treatment or relapse rates³⁷. However, the incidence of adverse events was significantly higher in the patients receiving cyclosporine compared to the other two cohorts.

Lapidoth et al. reported a study of 16 PV patients treated with prednisone 60-80 mg/day and cyclosporine 5 mg/kg/day and compared the outcome with a historic control group of 15 patients, treated with prednisone 120 mg/day on a tapering schedule.⁵⁰ The combined therapy cohort achieved clinical remission in a shorter timeframe than the historic control group, and the cessation time for new blister formation was also significantly shorter in the combined therapy cohort. The cohort receiving cyclosporine also had significantly shorter hospital admissions and a lower mean cumulative steroid dose, suggesting a steroid-sparing role of cyclosporine.

Barthelemy et al. published a study of nine PV patients treated with different regimens of cyclosporine and prednisone.⁵¹ The four patients treated with cyclosporine alone demonstrated no clinical improvement after 2 weeks. In four patients who showed no clinical improvement after 2 months of treatment with prednisone (>1 mg/kg/day), the addition of cyclosporine induced the clearing of lesions within 3 weeks, but three of four patients relapsed upon tapering of cyclosporine. One patient treated with prednisone 0.6 mg/kg/day and cyclosporine 6-8 mg/kg/day improved under the combined therapy but relapsed when the steroid dose was tapered.

Mobini et al. described a group of 6 PV patients with severe recalcitrant disease successfully treated with high dose prednisone and cyclosporine 1-3 mg/kg/day.⁵² Clearing of 'most lesions' occurred 16-20 weeks after cyclosporine therapy was initiated and discontinued after 1-2 years with no relapses reported over a 5-year follow-up.

Given the small number of RCTs evaluating cyclosporine in pemphigus, it is difficult to make firm conclusions from this evidence. Some of the studies were evaluating the wrong outcome measure for a steroid-sparing drug (i.e. time to disease control), as that occurs early because of the steroid therapy. The important outcome measure for a steroid-sparing agent is the proportion of patients eventually achieving complete remission on minimal therapy and this was not used as the primary outcome in these studies. Hence, whether cyclosporine is useful in pemphigus is still an open question. Our practice has been to use other steroid-sparing agents first, but cyclosporine should not be completely ruled out on the basis of the above.

Methotrexate

No controlled trials have been conducted investigating the efficacy of methotrexate in pemphigus. Early case series reported methotrexate as effective in disease control, however the therapy has been abandoned in recent years because of concerns about adverse effects. However, this may have resulted from the high dosages employed in combination with high dose corticosteroids.

In a series of nine patients with active PV, Smith and Bystryn reported the use of methotrexate 10-17.5 mg/week in combination with prednisone 20 mg/day.⁵³ In six of nine patients, steroid therapy could be discontinued within 6 months without any flare in disease activity, however all patients relapsed once methotrexate therapy was ceased. Adverse events were mild.

Mashkilleyson reported 53 patients with PV treated with prednisone 60-200 mg/day and methotrexate 25-50 mg/week.⁵⁴ Treatment was reported as 'effective' in 42 of 53 patients, 'ineffective' in nine of 53 patients and two patients withdrew because of adverse events. There were no changes in transaminases and liver biopsies performed after every cumulative 1.5 g of methotrexate were unremarkable. A steroid-sparing effect was observed. The most common adverse effect was infection. In this case series, 28 of 185 patients died, but the number of participants receiving methotrexate was not reported.

There is insufficient evidence to draw conclusions regarding the role of adjuvant methotrexate in pemphigus. Anecdotally, in clinical practice in Australia, methotrexate is used by dermatologists who report some success. Now that outcome measures have been defined, it would be good to see RCTs of methotrexate with prednisone versus placebo with prednisone, in a country such as Iran or India where there are many PV patients, to see if methotrexate were useful as a steroid-sparing agent in PV.

Chlorambucil

One small retrospective case series has been reported investigating chlorambucil therapy.⁵⁵ In the study, nine pemphigus patients (7PV, 2PF) were treated with chlorambucil and prednisone and six of nine patients demonstrated clinical improvement. The study suggests that chlorambucil may be a potential adjuvant in pemphigus when other immunosuppressants fail, but no recommendation can be made of its utility on this small series alone.

Gold

Gold is one of the oldest therapeutic agents, exerting anti-inflammatory properties and influencing humoral and cellular immunity. As it has a delayed onset of action, it is normally administered as an adjuvant therapy. One controlled study and a number of case series were identified.

Auad et al. reported a blinded, controlled trial of adjuvant gold in 30 PF patients.⁵⁶ Patients were initially

stabilized on corticosteroids, then gold 3 mg/day or placebo was administered. Nine of 30 patients did not complete the trial, and intention to treat analysis was not performed. The results of 10 patients treated with gold and 11 in the placebo cohort were reported, with a mean follow-up of 4 years. At 12 months, a steroid-sparing effect was seen with mean steroid dose of 37 mg/day in the placebo group and 5.5 mg/day in the gold arm. Four patients in the gold arm experienced mild complications, including diarrhea, and proteinuria.

Sutej et al. reported a prospective case series of six PV patients, four of whom had new onset disease.⁵⁷ Patients were treated with intramuscular gold thiomolate 50 mg and prednisone. All patients improved, with four of six patients tapering steroids below 15 mg/day, and 2 of 6 patients able to discontinue steroids. The regimen was well tolerated.

Pandya and Dyke reported 26 pemphigus patients with mild disease treated with intramuscular gold over 10 years.⁵⁸ Patients were treated with intramuscular gold thiomolate 50 mg weekly until disease control was established, and monthly injections thereafter for 4 months. Four patients were treated with gold monotherapy and 22 were treated with combined prednisone and gold. Response to therapy was reported in 22 of 26 (85%) patients, with a reduction of blisters and ability to taper steroids to <20 mg/day. Remission was reported in 11 of 26 patients who were able to discontinue steroids and four of these patients were able to discontinue all treatment. Four of 26 patients did not respond. There was no mortality, but adverse effects were noted in 11 of 26 patients, including proteinuria, eosinophilia, and "cutaneous reactions."

Iranzo et al. reported a case series of 13 patients with refractory PV treated with prednisone and gold.⁵⁹ Intramuscular auruothiomalate 50 mg weekly was administered with prednisone 7.5-100 mg, with 3 patients receiving concomitant intravenous immunoglobulin 400 mg/kg/day for 5 consecutive days once a month. Complete long-standing remission was achieved in seven of 13 patients and partial remission in seven of 13, with the remaining two of 13 ceasing treatment because of adverse effects (proteinuria and a cutaneous abscess with severe granulopenia). In 11 of 13 patients, the prednisone dose was halved.

Poulin et al. reported 13 PV patients treated with prednisone and intramuscular gold thiomolate or aurothioglucose 50 mg administered weekly.⁶⁰ In the retrospective series, seven of 13 patients achieved complete resolution of lesions and ceased all treatment after a mean of 18.3 months, although two of seven subsequently relapsed. Thus, five of 13 patients had remission at a mean follow-up of 48.8 months. Two patients demonstrated no clinical benefit from gold and three of 13 patients responded to the treatment, but therapy was stopped because of adverse effects – proteinuria, eosinophilia, mild leukopenia, and urticaria – all resolving upon cessation of gold.

Penneys et al. reported on the long-term follow-up of 18 patients treated with gold.⁶¹ The treatment regimen was the

same as that used by Poulin described above. Eight of 18 patients had clinical resolution of lesions and were able to stop all treatment after a mean of 37.3 months of gold therapy. Remission had been sustained in these eight patients during a follow-up period of 8-34 months. Seven of 18 patients improved, but required maintenance therapy. Two patients discontinued gold because of adverse events, and one patient was lost to follow-up. Adverse events reported included nephrotic syndrome, proteinuria, dermatitis, erythema nodosum, and agranulocytosis.

Gold may be considered as a possible treatment option when other adjuvants cannot be employed. The case series in the literature indicate that the majority of patients on gold therapy demonstrate clinical improvement, with many able to stop treatment, and a steroid-sparing effect has been reported. At the same time, adverse effects are common, albeit relatively mild, and often precede clinical improvement which needs to be considered with using gold therapy.

Dapsone

Dapsone has been evaluated in one RCT of 19 recalcitrant PV patients reported by Werth et al.⁶² Patients were randomized to receive maintenance steroids plus either dapsone 125-150 mg/day (n=9) or placebo (n=10). In the dapsone cohort, five of 9 patients were able to taper their steroid dose below 7.5 mg/day compared to three of 10 in the placebo cohort, although this was not statistically significant. The authors presented some trends favoring the use of dapsone, but statistical significance was never reached. This did not exclude a beneficial effect because of the low power of the study. Adverse events included paraesthesia and methemoglobinemia.

Heaphy et al. reported the use of dapsone in a retrospective case series of nine PV patients who were steroid-dependent or had poor disease control.⁶³ Patients were receiving glucocorticoids and immunosuppressants in addition to dapsone titrated to 125-150 mg/day. After eight months, seven of nine patients were able to reduce their prednisone dose by 84% to <7.5 mg/day and two of seven were able to discontinue steroids. No response was seen in two of nine patients who had poor disease control at baseline.

Basset et al. reported a case series of nine newly diagnosed patients receiving dapsone 200–300 mg/day.⁶⁴ Five patients, all with mild to moderate disease, responded with at least a 50% decrease in the extent of their disease within 15 days of starting therapy. Four patients did not respond. Three patients discontinued dapsone because of adverse events, including hemolytic anemia, toxic hepatitis, and methemoglobinemia.

Dapsone appears to benefit some PV patients in the maintenance phases of their disease, however as there is little evidence to support the use of dapsone in pemphigus, it is difficult to evaluate its utility.

Tetracyclines/Nicotinamide

The evidence for the use of tetracyclines and nicotinamide in pemphigus is derived from small case series.

Calebotta et al. reported a prospective series of 13 hospitalized patients with PV treated with tapering regimens of tetracycline 2 g/day and prednisone 0.5-1 mg/kg/day and compared the study group with a historic cohort of seven pemphigus patients treated with prednisone and azathioprine.⁶⁵ All patients in the study cohort achieved cessation of blister formation within 5.5 days compared to 23.7 days in the control cohort. The study cohort also had fewer new lesions after 2 weeks, could taper their steroid doses faster, and had short hospital admissions that were all statistically significant.

Alpsoy et al. reported 15 patients with pemphigus (11PV, 4 PF) treated with tetracycline 2 g/day and nicotinamide 1.5 g/day over 2 months.⁶⁶ Five patients were newly diagnosed and 10 had previously been treated with corticosteroids and/or immunosuppressants. All patients had active disease. At 2 months, two of 15 had complete healing, four of 15 had 50% of lesions healed, and nine of 15 had no response. Three of 15 patients had mild gastrointestinal upset.

Chaffins et al. reported 11 pemphigus patients (6PV, 5PF) treated with nicotinamide 1.5 g/day and tetracycline 2 m/day with five of 11 on concurrent prednisone (2.5-30 mg/day).⁶⁷ After 8 weeks of treatment, five of 11 had complete resolution, 4 of 11 had >50% of lesions resolved, and two of 11 had no response. Four patients experienced mild gastrointestinal upset and one patient developed a morbilliform eruption. Gaspar et al. reported 10 patients (7PV, 3 PF) with active disease treated with minocycline 100 mg/day as an adjuvant.⁶⁸ Nine of 10 patients were concurrently treated with prednisone 10-40 mg/day and five patients concurrently received azathioprine 100-200 mg/day. Assessed subjectively, four of 10 patients had complete lesion resolution, two of 10 improved and four of 10 had no response, and a steroid-sparing effect was observed. Candidiasis occurred in nine of 10 patients and one of 10 developed hyperpigmentation.

The case series present inconsistent evidence regarding the use of antibiotics and nicotinamide in pemphigus. They could be considered as adjuvant treatment in mild cases, but further research including controlled trials is warranted to elicit their utility in this setting.

Plasmapheresis

Plasmapheresis is hypothesized to remove pathogenic autoantibodies and has been used in refractory cases of pemphigus. The utility of plasmapheresis is controversial with the results of one RCT ostensibly opposing those of small case series.

Guillaume et al. randomized 40 previously untreated pemphigus patients to prednisolone monotherapy

(0.5-2 mg/kg/day) (n=18) or prednisolone plus 10 large-volume plasma exchanges (55 mL/kg/exchange) over 4 weeks (n=22).⁶⁹ No differences were observed between cohorts with respect to clinical improvement, cumulative steroid dose or autoantibody titer. Four patients in the plasmapheresis cohort died of sepsis or thromboembolism.

These results differ to the outcomes reported in the case series and reports on plasmapheresis.

Tan-Lim and Bystryn reported a retrospective case series, comparing 11 patients (9PV, 2F) treated with plasmapheresis (1000-2000 mL/exchange; 5-12 exchanges over 10-24 days), corticosteroids (70-240 mg/day) and immunosuppressants (azathioprine or cyclophosphamide), with 11 patients (9PV, 2F) treated with steroids and immunosuppressants alone.⁷⁰ The average autoantibody titer decreased by 83% after 3 weeks of treatment in the plasmapheresis compared to a decrease of 18% in the historic control.

Roujeau et al. described a retrospective case series of 10 patients (2 PF, 8 PV) treated with massive volume plasmapheresis (3000-5000 mL/exchange).⁷¹ Patients received treatment with prednisone 0.1-2.5 mg/kg, and concurrent cyclophosphamide, azathioprine, or chlorambucil. Plasmapheresis was administered 2-3 times per week with 3-20 sessions per patient over 1-16 weeks. Rapid improvement was observed in six of 10 patients with no new blister formation after four treatments, however, three of six subsequently relapsed. Transient improvement was seen in two of 10 patients and no improvement observed in two of 10. Adverse events included thrombocytopenia, hypocalcaemia, urticaria, fever, hypotension, and two patients suffered acute hepatitis. Sondergaard et al. have reported the use of plasmapheresis in eight patients (7PV, 1PF) in combination with prednisone 30-120 mg/day and adjuvant therapy.⁷² At baseline, two of eight patients were lesion-free, three of eight were newly diagnosed and three of eight had pre-existing disease. In four of eight cases, pemphigus had been resistant to conventional therapy. Patients were treated with massive volume plasmapheresis (1500-3000 mL/exchange) 1-2 times per month for 5-73 months. All patients were in clinical remission within 2 months of therapy and remained in remission for 40-94% of the treatment period. A significant steroid-sparing effect was demonstrated and side-effects were rare and transient.

The role of plasmapheresis in pemphigus is controversial. The RCT by Guillaume et al. provides the best quality of evidence, although it doesn't correspond to the case reports in the literature. Some have argued that concurrent immunosuppressive agents are required to prevent rebound antibody synthesis during plasmapheresis,⁷⁰ which may explain the poor efficacy of plasmapheresis in the trial. Plasmapheresis may be considered for rapid control of severe or recalcitrant pemphigus but only in conjunction with immunosuppression to reduce rebound of autoantibodies.

Intravenous Immunoglobulin

Intravenous immunoglobulin (IVIg) is being increasingly employed in the treatment of recalcitrant pemphigus. There have been two RCTs and several case series describing its use.

Amagai et al. have recently published a double-blinded, multicenter RCT of 61 pemphigus patients randomized to infusions of IVIg 400 mg/kg/day ($n=21$) or 200 mg/kg/day ($n=20$), or placebo ($n=20$) over 5 consecutive days.⁷³ A particular protocol was established and the success of therapy was based on the time until they had to deviate or 'escape' from the protocol. A dose-response relationship was observed amongst the three cohorts with the time to escape from the protocol significantly prolonged in the 400 mg cohort compared to placebo. Both the 200 mg and 400 mg cohorts were reported to have significant decreases in pemphigus activity scores and autoantibody titers from baseline, while no decrease was observed in the placebo cohort. No significant difference was observed between cohorts in terms of safety profile at 85-day follow-up. Due to the short-term nature of the study and outcome measure being time to escape from the protocol, rather than the proportion of cases in complete remission on no therapy or minimal therapy, it is still difficult to be sure that IVIg has a high cost-benefit ratio compared to other options. Another randomized-controlled crossover trial of IVIg was conducted in a single patient with severe PV comprising of two phases of 6 months of treatment with either IVIg or placebo infusion with prednisolone and azathioprine therapy maintained throughout the study.⁷⁴ Although this study was clearly limited by having a single subject, the mean dose of prednisolone was significantly lower during the treatment phase of the cross-over and the mean subjective patient disease scores and pemphigus autoantibody titers also improved. Ideally there should be more studies of IVIG conducted along these lines.

The largest case series is reported by Ahmed in which 21 patients with severe refractory PV treated with IVIg 2000 mg divided into 3 doses administered over 3 consecutive days, given at 4 week intervals until all lesions healed.⁷⁵ Improvement was observed after 4.5 months on average and the mean number of cycles administered was 18 (ranging from 14-34). It was reported that in all 21 patients, prednisone and adjuvant therapy could be discontinued, with remission achieved for an average of 20 months (ranging from 13-73). Following treatment, participants were reported to receive significantly lower doses of prednisone, fewer side recurrences and relapses, fewer and shorter hospital admissions and improvements in quality of life compared to before IVIg therapy. Another series by Baum et al. employed a similar treatment protocol to Ahmed in 12 patients with severe PV.⁷⁶ In 10 of 12 patients, treatment with IVIg allowed a reduction in prednisone dose compared to baseline, with six of 12 achieving clinical remission after 6 cycles. A partial response was observed in four of 12 patients and no response reported in two of 12. The results are concordant with the other series published in the literature.

IVIg appears to be an effective and safe treatment in recalcitrant pemphigus patients who have failed conventional therapy. Although expensive, it has a demonstrable corticosteroid-sparing effect and has been reported to have a rapid effect on disease activity, albeit transient at times. It appears that IVIg functions well as an adjuvant therapy in recalcitrant pemphigus, with repeated courses necessary to sustain benefit.

Immunoabsorption

Immunoabsorption is a relatively new treatment, which unlike plasmapheresis, specifically removes particular plasma components such as pathogenic immunoglobulins. The evidence for this therapy is derived solely from case series. Lüftl et al. reported a series of nine pemphigus patients (7PV, 2PF) treated with immunoabsorption in addition to their regular immunosuppressive therapy.⁷⁷ Evaluation by ELISA revealed a 30% reduction of pathogenic IgG antibodies after a single immunoabsorption treatment, and all patients demonstrated clinical improvement. Eming et al. reported 4PV patients and 2 PF patients treated with immunoabsorption adjuvant to their regular immunosuppressive medications.⁷⁸ Immunoabsorption was performed for 4 consecutive days every 4 weeks, representing one treatment cycle, with immunoglobulin 10g administered each cycle. The authors reported that a single immunoabsorption cycle reduced anti-Dsg1 and anti-Dsg3 antibodies by an average of 50-70% with all patients demonstrating rapid clinical improvement. Schmidt et al. reported five patients (4PV, 1PF) treated with 3 days of immunoabsorption, representing one cycle, with pulse dexamethasone and cyclophosphamide and oral methylprednisolone administered between cycles to minimize antibody resynthesis.⁷⁹ A single cycle was reported as reducing ELISA readings by 80-90% and all patients were in clinical remission at follow-up 13-116 weeks after initiating treatment. A similar immunoabsorption protocol was employed by Shimanovich et al. in a series of nine PV patients, with oral methylprednisolone and either azathioprine or mycophenolate mofetil employed instead of dexamethasone/cyclophosphamide therapy.⁸⁰ A single cycle was reported to reduce autoantibody titers by 75% and patients remained free of clinical disease for up to 26 months after treatment was discontinued.

These small case series are promising, but to date have focused their outcome measures on autoantibody levels with clinical outcomes assessed before the newer disease extent scales were developed. Further studies are warranted, ideally evaluating the clinical effects of immunoabsorption objectively.

Rituximab

Rituximab is an anti-CD20 humanized monoclonal antibody causing transitory B-cell depletion reserved for

patients with pemphigus that is unresponsive to conventional therapies or to patients in whom these drugs are contraindicated. Several case reports and a number of small series describe patients treated with pemphigus on a regimen of four weekly infusions of rituximab 375 mg/m.²

Joly et al. prospectively studied 21 patients (14PV, 7PF) treated with rituximab in addition to their regular immunosuppressive therapy.⁸¹ At 34 months, 18/21 (86%) patients were disease free and eight of these patients were no longer on systemic therapy. A steroid-sparing role was demonstrated and autoantibody titers had decreased in those patients who had achieved remission. Cianchini reported 12 patients (10PV, 2PF) with severe pemphigus treated with rituximab.⁸² All patients experienced disease control 1 month after treatment, with 4 of 12 (33%) having complete remission for up to a year. Antibody titers were shown to decline over 6 months and no adverse effects were observed. Antonucci described five PV patients who achieved complete remission for 12 months after rituximab treatment associated with a decline in antiepidermal antibodies.⁸³ Goh et al. reported a prospective study of 5 PV patients treated with rituximab.⁸⁴ At 13 months, one of five had complete remission with cessation of steroids, two of five achieved remission while continuing on medication and two of five were considered to have a partial remission.

Most of the patients in these case series have responded to rituximab with resistant lesions often cleared in 1-4 months. Rituximab may be a valuable treatment for recalcitrant pemphigus but further studies are warranted and further monitoring for long-term safety.

Pimecrolimus

Pimecrolimus is a topical immunomodulator with a calcineurin inhibitory effect encumbering T-cell and mast cell activation as well as the synthesis of a number of cytokines. The efficacy of the agent has been established in inflammatory disorders, most notably atopic dermatitis, but also more resistant problems, such as oral lichen planus,⁸⁵ and there has been one double-blinded, controlled trial investigating its efficacy in pemphigus.⁸⁶ Eleven patients with confirmed PV under treatment with prednisolone and azathioprine who had bilateral symmetrical oral lesions had all right or left-sided lesions randomized to treatment with either pimecrolimus 1% cream or placebo for 30 days. Overall, 31 lesions were treated with pimecrolimus and 31 were treated with placebo and at the conclusion of the study, there was a significant difference in the epithelial index of lesions in favor of the pimecrolimus. These results and encouraging and future studies could evaluate the efficacy of pimecrolimus with larger cohort numbers as well as lesions at other sites.

Topical epidermal growth factor

The efficacy of topical epidermal growth factor (EGF) has been evaluated in a double-blinded RCT of 20 PV patients.⁸⁷ Patients had similar, symmetrical lesions treated with either epidermal growth factor 10 µg/g in silver sulfadiazine cream or silver sulfadiazine cream alone. Lesions treated with topical EGF healed in a median of 9 days compared to control lesions which healed in a median of 15 days, with

What We Know

- The best evidence-based algorithm for the management of pemphigus is yet to be established.
- Systemic corticosteroids are the mainstay of treatment. Regimens of oral corticosteroid at around 1 mg/kg/day appear to be as effective as higher doses and much safer.
- Azathioprine and mycophenolate mofetil appear to be the adjuvant therapies of choice based on their steroid-sparing effects and safety-profiles. Oral cyclophosphamide may be considered as an alternative, as it has a good efficacy but unfavorable side-effect profile.
- Adjuvant cyclosporine is of limited use in pemphigus.
- There is insufficient evidence to assess the utility of methotrexate, gold, dapsone, and tetracyclines in pemphigus.
- Plasmapheresis, IVIg, immunoabsorption, rituximab, topical pimecrolimus and topical epidermal growth factor are all promising therapies in pemphigus. Further studies are warranted to elucidate their exact role in the management of pemphigus.
- Further studies are warranted to ascertain the best approach to management in pemphigus, ideally as blinded, multicenter controlled trials with large patient cohorts and valid, objective outcome and disease extent measures.
- Low dose (1mg/kg/d) prednisone is as effective as higher doses of prednisone in inducing remission of pemphigus
- Adjuvant mycophenolate mofetil (MMF) shortens the time to complete remission on therapy and reduces steroid requirements
- Adjuvant azathioprine was steroid sparing in one study and no different in effectiveness to MMF in other studies
- IVIG appears to be beneficial in uncontrolled studies and one placebo-controlled study but needs further confirmation; it has a good safety profile.
- Rituximab appears effective in some recalcitrant cases of PV but has not been tested in by RCT
- Most studies in PV do not reach adequate power to give statistically significant results

TABLE 17-1—Therapies in Pemphigus and Their Evidence

Treatment	Evaluation	Level of Evidence	Strength of Recommendation
Oral corticosteroids	Optimum dosing unknown; but low-dose regimens ($\leq 1\text{mg/kg/day}$) show equivalent efficacy and better safety ²⁰ <i>First line treatment</i>	1B	I
Pulse i.v. steroids	No advantage demonstrated of adjuvant therapy over placebo ²³ <i>Consider in severe/recalcitrant disease</i>	1B	I
Azathioprine	Demonstrated steroid-sparing role ²⁷ Superiority over mycophenolate mofetil controversial ²⁹ <i>May be used adjuvantly for steroid-sparing effect</i>	1B 1B	I I
Mycophenolate mofetil	Demonstrated steroid-sparing role ^{27,32} Superiority over azathioprine controversial ²⁹ <i>May be used adjuvantly for steroid-sparing effect</i>	1B 1B	I I
Oral cyclophosphamide	No advantage demonstrated over steroid monotherapy ³⁷ <i>Consider if azathioprine/mycophenolate mofetil are unsuitable</i>	1B	I
Pulse i.v. cyclophosphamide	Demonstrated steroid-sparing role ²⁷ <i>Consider in severe/recalcitrant disease</i>	1B	I
Cyclosporin	Adjunctive cyclosporin has no demonstrated advantage in pemphigus ^{37,49} <i>Cannot be advocated in pemphigus</i>	1B	I
Methotrexate	Early case series promising, but concerns exist regarding adverse effects ^{53,54} <i>Limited data available to establish role of therapy</i>	4	III
Chlorambucil	One small retrospective case series suggested the drug may be useful ⁵⁵ <i>Limited data available to establish role of therapy</i>	4	III
Gold	Many patients demonstrate clinical improvement and steroid-sparing role reported ⁵⁶ <i>An alternative to traditional adjuvants</i>	2B	II-1
Dapsone	Small RCT evaluating use of adjuvant dapsone did not reach significance ⁶¹ May benefit patients in maintenance phase of disease ^{62,63} <i>An alternative to traditional adjuvants</i>	1B 4	I III
Tetracyclines/ Nicotinomide	Variable efficacy reported ^{65–68} <i>An alternative to traditional adjuvants in mild pemphigus</i>	4	III
Plasmapheresis	No advantage demonstrated over steroid monotherapy ⁶⁹ <i>Further studies warranted; results of RCT contrary to earlier work</i>	1B	I
IVIg	Demonstrated role in decreasing disease activity and antibody titres ^{73,74} <i>Consider if traditional adjuvants are unsuccessful</i>	1B	I
Immunoabsorption	Shown to decrease antibody titres with many patients showing clinical improvement ^{77–80} <i>Further studies warranted evaluating clinical improvement</i>	4	III
Rituximab	Demonstrated steroid sparing role with efficacy demonstrated in recalcitrant pemphigus ^{81–84} <i>Consider if traditional adjuvants are unsuccessful</i>	4	III
Pimecrolimus	Significant improvement in oral lesions over placebo ⁸⁶ Further studies warranted evaluating cutaneous efficacy	1B	I
Topical epidermal growth factor	Improved lesion healing observed ⁸⁷ <i>Further studies warranted.</i>	1B	I

the difference found to be significant. Further studies are required to confirm these promising results before making an assessment of topical EGF in pemphigus.

CONCLUSION

As a rare disease, there is a paucity of good-quality evidence regarding interventions in pemphigus (Table 17-1). Well-designed, randomized-controlled trials are scarce and because of the previous deficits in uniform outcome measures in pemphigus, it is difficult to compare the efficacy of modalities across different studies. Further studies using the consensus definitions for outcome measures and assessment tools are necessary to ascertain the best approach to management in pemphigus. Ideally, these should be double-blind, randomized-controlled trials with large patient cohorts, using valid, objective outcome measures that can provide an evidence-based approach to the treatment of pemphigus.

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Treatment of Dystrophic Epidermolysis Bullosa

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INTRODUCTION

Dystrophic epidermolysis bullosa (DEB) belongs to a family of inherited bullous diseases in which the blisters heal with scars.¹ The pathogenesis of DEB involves the anchoring fibrils, structures that emanate from the epidermal-dermal junction (EDJ) basement membrane zone (BMZ), and attach to the high papillary dermis. These structures consist of a skin specific collagen called type VII collagen (C7).²⁻³ Normal anchoring fibrils with normal functioning are necessary for adherence between the epidermis and dermis. Approximately 25 – 30% of the normal complement of functioning anchoring fibrils is necessary to keep the epidermis adhered to the dermis.⁴ When anchoring fibrils fall below this percentage, the patient experiences skin fragility and subepidermal bullae over trauma-prone extensor surfaces that heal with milia and scar formation.

There are two ways that anchoring fibrils and their function can be perturbed and lead to clinical skin disease. The first occurs in DEB in which there is a gene defect in the *COL7A1* gene that encodes for the C7 alpha chain, a large molecule of 290,000 daltons. The second arises in patients with autoimmune dysregulation who produce IgG autoantibodies to type VII (anchoring fibril) collagen.⁵⁻⁶ The IgG autoantibodies deposit on anchoring fibrils and leads to their dysfunction or destruction by mechanisms that are not well understood. These patients have acquired EB, so-called epidermolysis bullosa acquisita (EBA). Whether it is genetic DEB (inherited by autosomal dominant or recessive patterns) or an acquired autoimmune bullous disease, such as EBA, these anchoring fibril-centered diseases have similar phenotypes – skin fragility, subepidermal bullae in trauma-prone areas of skin, erosions, milia formation, and scars. Disease severity is variable, but in general, EBA is a

less severe phenotype than recessively inherited DEB with two abnormal alleles.

With regard to therapy, there is very little “evidence-based” therapy for either DEB or EBA.

THERAPY FOR EPIDERMOLYSIS BULLOSA

Epidermolysis bullosa is a disease that has been described prior to the turn of the last century. However, it is a very rare disease. For that reason, there has never been a single controlled therapeutic trial of any medication or device for EBA. To further complicate matters, although all EBA patients have IgG autoantibodies that bind to C7 and anchoring fibrils, the clinical phenotype is anything but uniform. The most common presentation is a relatively noninflammatory, mechanobullous disease that is reminiscent of genetic DEB. However, in a subset of patients, the disease can be highly inflammatory and mimic bullous pemphigoid or cicatricial pemphigoid.⁷⁻⁸ To date, there is no good explanation why there are these variable phenotypes of EBA. Nevertheless, designing a blinded, placebo-controlled therapy trial for EBA is simply unfeasible and has never been done. Therefore therapy for EBA has been “non-evidence based” and has relied simply on anecdotal reports and small case series. Based on these reports, the currently available treatment for EBA is unsatisfactory. Nevertheless, EBA patients may benefit from treatment with the following¹²⁻²²:

1. Immunosuppressive agents
2. Dapsone
3. Colchicine
4. Photophoresis
5. IVIG
6. Biologics (such as rituximab)

Systemic prednisone has very limited value in the noninflammatory, mechanobullous form of EBA. These patients should be advised to avoid trauma to minimize trauma-induced vesiculation and scarring.

THERAPY FOR RECESSIVE DYSTROPHIC EPIDERMOLYSIS BULLOSA

Recessive dystrophic epidermolysis bullosa (RDEB) is a genetic disease caused by a defect in the gene that encodes for a skin-specific collagen called C7. The patients are born with an incurable skin disease, which is manifest by extreme skin fragility, blisters, erosions, and scarring. Other findings include dystrophic fingernails, fibrotic adherent digits, small pearl-like epidermal cysts (milia), mouth and esophageal erosions, poor dentition, and stenosis of the upper one-third of the esophagus caused by chronic wounding and healing at that site. In the third decade of life, RDEB patients frequently develop aggressive and often fatal squamous cell carcinomas in their chronic wounds²³⁻²⁵. There is no current cure for RDEB.

C7 in skin is organized into structures called anchoring fibrils. These structures are large and range in size from 300 nm – 800 nm. They are localized at the interface between the epidermis and dermis and are known to be critical for normal adherence of the epidermis onto the dermis.²⁶

For some time in the past, the prevailing hypothesis in RDEB was that the dermal fibroblasts (or other cell type) synthesized too much collagenase, leading to the degradation of type VII (anchoring fibril) collagen. Therefore, clinicians focused on therapy that could decrease the local amount of collagenase in the skin with the hope that anchoring fibrils would not be degraded. One known collagenase inhibitor is phenytoin (Dilantin). In one small study, systemic phenytoin was given to RDEB patients, and it appeared that these patients developed fewer new lesions, healed older lesions more rapidly, and had overall, better epidermal-dermal adherence with fewer wounds.²⁷ Nevertheless, a larger controlled study comparing phenytoin to placebo showed that the phenytoin was no better than placebo²⁸.

The idea that RDEB was caused by some type of intrinsic increase in collagenase was dispelled when several investigators showed that RDEB was caused by defects in the gene that encodes for C7, the COL7A1 gene. This discovery opened the possibility for gene therapy as an approach of curing RDEB. In theory, the keratinocytes taken from an RDEB patients' skin biopsy could be placed into tissue culture, engineered to correct the gene defect, grown into large sheets, and then transplanted as sheets back onto the patient. Cultured keratinocyte autografts have been successfully transplanted back onto severely burned patients, both adults and children, with success.²⁹⁻³¹ Nevertheless, these keratinocyte sheets are thin and fragile,

and considerable attention needs to be paid to preparing the transplant wound site, applying the cultured autograft, carefully and gently bandaging the patient, and then immobilizing the patient post-transplantation. While feasible, it is logically difficult and some percentage of the transplanted skin is lost.

Both human keratinocytes and human dermal fibroblasts can make C7.³²⁻³³ Thus, it is possible to gene-correct either RDEB keratinocytes or fibroblasts. RDEB keratinocytes and fibroblasts exhibit abnormal morphology, substratum attachment, cell motility, and proliferative potential.³⁴ When these cells are gene-corrected to synthesize and secrete C7, all of these cellular parameters normalize. The cells behave and look like normal skin cells.³⁴ Engineering human fibroblasts offers advantages over keratinocytes, primarily because of their relative ease in culturing and handling. Fibroblasts can be grown with an additional cell for co-culture and passaged over 30 doublings, while keratinocytes are much more finicky and can often only be passaged five to eight times. Therefore, because of these advantages, gene corrected fibroblasts have also become a target for treatment of RDEB.³⁵⁻³⁶ In fact, it has been shown by us and by others that if you intradermally inject gene-corrected RDEB fibroblasts into RDEB skin that has been transplanted onto an immunosuppressed animal, the cells take up residence in the transplanted skin upper dermis, and act like small C7 factories that synthesize and export the protein into the extracellular space of the transplanted skin.³⁵⁻³⁶ Within the extracellular space, the fibroblast-derived C7 will bind to the BMZ between the epidermis and dermis and form anchoring fibrils. The new anchoring fibrils in the RDEB graft then induce good adherence of the epidermis to the dermis and the phenotype of the RDEB graft (skin fragility and blistering) is reversed³⁵⁻³⁶. We have recently shown that gene-corrected RDEB human fibroblasts injected into the vein of an immunosuppressed mouse will migrate to exogenously induced wounds. There, they set up residence in the dermis of the mouse's healing wound and synthesize and export human C7³⁷. We have called this "Cell Therapy" for RDEB.

Recently, the research team of Dr. John McGrath in Great Britain has tried "Cell Therapy" for patients with RDEB with some success.³⁸ Patients received fibroblast injections of normal dermal fibroblasts from a relative, an unrelated donor, or, as a control, themselves. All of the patients tested had RDEB, but made some endogenous C7 at their EDJ. When patients were injected intradermally with normal dermal fibroblasts, the C7 at their EDJ increased, whereas there was no increase when they were injected with their own fibroblasts. In addition, the investigators noted that there was improved epidermal-dermal adherence in the patients treated with normal dermal fibroblasts. While this was encouraging, there was one finding that was both puzzling and less straightforward. When the investigators determined the source of the increased C7 at the EDJ, they found that it came from the patients' cells and was

actually mutated C7 rather than normal C7. The investigators speculated that the injection of normal dermal fibroblasts stimulated the patient's keratinocytes and fibroblast to synthesize and secrete more mutated C7, which homed to the EDJ. That is, it did not appear that the injected normal fibroblasts were contributing C7 to the patient's EDJ. So, while there was a positive therapeutic result, the underlying mechanism toward that result was not what had been expected and was somewhat disappointing.

Using RDEB skin equivalents grafted onto hairless immunosuppressed mice, it was also shown that viral vectors expressing the full-length C7 alpha chain could be intradermally injected into the RDEB skin.³⁹ Both fibroblasts and endothelial cells in the RDEB skin grafts took up the injected viral vectors. These RDEB endogenous cells then expressed normal C7 and secreted it into the local skin environment. In the extracellular spaces in the high papillary dermis, the extracellular C7 bound to the basement membrane at the EDJ of the RDEB skin and produced anchoring fibrils. We called this therapeutic strategy "**Vector Therapy**." Similar to "**Cell Therapy**," vector therapy also resulted in a great amount of linear C7 and anchoring fibrils at the EDJ of the RDEB skin and greatly improved epidermal-dermal adherence.

Vector Therapy

Vector therapy has also been shown to be beneficial in an RDEB-like animal model. This murine model consists of knockout mice unable to make C7.⁴⁰ These mice have a severe blistering disease of their skin and oral mucosa. The mice only live for a few days. Nevertheless, when these animals are injected intradermally with a lentiviral vector expressing the normal human C7 alpha gene, new blistering decreases, the mice live longer and the mice have human C7 and human anchoring fibrils at their EDJ. Their RDEB phenotype is essentially reversed.

One potential advantage of vector therapy is that the patient's own endogenous cells become the papillary dermal "cell factories" synthesizing and secreting normal C7, and no foreign cells are used. Donor-recipient HLA matching issues become moot. While an effective therapy in animal models, this therapy does involve injecting a foreign virus into the patient and has the potential for an untoward immune response. It also has an unlikely but possible side effect of the viral vectors recombining into an active virus and infecting the patient.

Another therapeutic strategy to consider is simply to administer the C7 protein to patients.⁴¹ We know that normally, C7 is synthesized and secreted into the extracellular space of the skin by keratinocytes and fibroblasts. Once this large matrix molecule is in the extracellular space, there are extracellular mechanisms by which the C7 binds to the BMZ in the EDJ. Presumably, this happens by protein-to-protein interactions and adhesion. The BMZ is rich in type IV collagen and laminin-5, and C7 has binding

domains for both of these matrix molecules.⁴²⁻⁴³ Once C7 molecules are selectively concentrated at the BMZ, they are capable of organizing themselves into anchoring fibril structures. Using the RDEB-like mouse model mentioned above, we demonstrated that we could reverse their RDEB phenotype by injecting the animals intradermally with human C7 protein.⁴⁴ The injected human protein became incorporated into the C7-null mice skin at the EDJ and created human anchoring fibrils. Not only did the knock-out RDEB mice now have human C7 and anchoring fibrils at their EDJ, but they lived longer and no longer had skin bullae. We call this approach "**Protein Therapy**."

In summary, we have in vitro studies and in vivo animal studies that demonstrate the feasibility of treating RDEB patients with cell therapy, vector therapy or protein therapy. However, except for the small study by the McGrath group detailed above using cell therapy, there are no other human RDEB trials that have shown a therapeutic benefit for RDEB patients. Therefore, strong evidence-based medicine treatments for RDEB are lacking. Nevertheless, promising clinical trials are currently underway. The group at Stanford University, led Dr. Paul Khavari and Dr. Alfred Lane are pursuing ex vivo therapy for RDEB patients and plan to transplant these patients with gene-corrected, cultured, autologous, keratinocyte sheets. The group in England headed by Dr. John McGrath is continuing to study cell therapy with more patients and using various modifications of their originally published protocol. Investigators at the University of Minnesota and Columbia University are performing clinical trials with RDEB patients in which the patients are treated with bone marrow and stem cell transplants. Although not yet published, it appears that at least one RDEB child was treated very successfully by this approach. Unfortunately, others had serious side effects including death. Lastly, the investigators at the University of Southern California are pursuing protein therapy and have designed a clinical study that will be initiated this year. They believe that there are lower intrinsic risks associated with protein therapy because it does not require exposure to viral vectors or foreign cells and does not carry the associated risk of bone marrow and stem cell transplantation. Protein therapy may also prove to be the most practical because it obviates the need for transplantation of cultures, meticulous wound care, and patient immobilization. However, there are many questions that still need to be answered regarding this and other C7-based therapies. It may be that RDEB patients with no endogenous C7 will produce antibodies to the newly introduced C7 during protein therapy (or vector therapy or cell therapy). The Federal Drug Administration has given protein therapy "orphan disease" status, which should allow it to be approved for use in humans with less regulatory hurdles. Clinical trials are necessary to validate these treatment options and determine what the effects of any newly formed antibodies to C7 will be.

What We Know

- DEB can be inherited or acquired
- A paucity of normal function anchoring fibrils is the common denominator
- DEB is very rare so no FDA-approved medications
- No known cure for inherited or acquired DEB
- No evidence-based studies to support DEB therapy
- For hereditary DEB gene therapy, cell therapy, Vector therapy and Protein
- Therapy is all-possible and works well in an RDEB-like knockout mouse model
- Protein therapy for hereditary DEB is probably the safest treatment to try first
- Therapy for acquired EB (EBA) is based solely on case reports

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Treatment of Alopecia Areata

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INTRODUCTION

No drug is currently approved by the U.S. Food and Drug Administration (FDA) for the treatment of alopecia areata, a complex genetic, immune-mediated disease that targets anagen hair follicles.¹ Alopecia areata is clinically characterized by round or oval patches of hair loss, loss of all scalp hair (alopecia totalis), loss of all body hair (alopecia universalis) or ophiasis pattern hair loss. Both males and females of all ages can be affected and there is no known race or ethnic preponderance. In alopecia areata, the hair follicle is not destroyed and maintains its potential to re-grow hair should the disease go into remission. It is estimated that alopecia areata affects between 4 and 5 million individuals in the United States.² Treatments have been evaluated in randomized trials and as with any autoimmune disease, spontaneous remission is common.

There is currently no cure for alopecia areata and no universally proven therapy that induces and sustains remission.³ Many therapies are available and current treatment choices are frequently based on disease extent, duration, and age of the patient.⁴ The option of not being treated is an alternative way of dealing with this disease.^{5,6}

EPIDEMIOLOGY

The prevalence of alopecia areata in the United States, as determined from the First National Health and Nutrition Examination Survey conducted from 1971 through 1974 was 158 per 100,000 persons, or roughly 0.1 to 0.2% of the population.⁷ From several studies published primarily in the American and British literature, the presence of severe nail abnormalities, atopy (asthma, allergic rhinitis, and atopic dermatitis), onset of extensive disease in children less than 5 years of age, as well as alopecia totalis or universalis lasting more than 2 years, have all been implicated as negative prognostic indicators.^{8,9}

Surveys from other parts of the world such as Kuwait, Northern India, Chandigarh India, Singapore, and Korea have revealed similar as well as slightly different associations.¹⁰⁻¹⁵ In a study from Kuwait, associations were similar to those reported in the western literature. Similar findings were also reported from Chandigarh, India except that

the association of atopy with a younger age of onset and severe alopecia areata was not confirmed. Different associations were reported from studies completed in Kuwait and Northern India. In a study of 10,000 consecutive new patients surveyed in Kuwait, a female preponderance was observed and infants constituted the largest group and in the study from Chandigarh, the age of onset, a positive family history for alopecia areata and associated atopic disorders were noted to have no influence on the extent and severity of the disease.

ETIOLOGY AND DIAGNOSIS

Alopecia areata is a complex genetic, immune-mediated disease that targets anagen hair follicles.¹⁻³ Transplantation studies in severe-combined immunodeficient (SCID) mice established that T-cell immunity is critical in the pathophysiology of this disease.¹⁶

A hallmark of alopecia areata is the histopathologic presence of peribulbar lymphocytes around anagen follicles. There is also some evidence to suggest that immune privilege is lost in alopecia areata.^{17,18a,18b} The peribulbar infiltrate in alopecia areata is frequently referred to as a "swarm of bees," particularly in patients with active disease. In patients with long-standing disease, this inflammatory process may be less obvious. Recent studies have demonstrated the expression of cytomegalovirus UL16-binding protein (ULBP) expression in lesional scalp of patients with active disease providing evidence for the involvement of both innate and acquired immunity in the pathogenesis of alopecia areata.¹ Nerves have also been implicated in the pathogenesis of alopecia areata and stressful life events and psychiatric disorders have been studied as they relate to both the onset and progression of alopecia areata.^{19,20} Genes, the immune and nervous systems continue to be active areas of research in alopecia areata.

Clinically, alopecia areata is quite straightforward to diagnose. Other hair diseases in the differential diagnosis for patchy disease include Tinea capitis and trichotillomania. The differential diagnosis for extensive alopecia areata includes popular atrichia as well as an ectodermal dysplasia. If the diagnosis is not straightforward, examination of a 4-mm scalp biopsy specimen may be beneficial.²¹

SEARCH METHODOLOGY

Searches were performed for the terms “alopecia areata,” “alopecia totalis” and “alopecia universalis with both “AND treatment” and “AND therapy” as modifiers on MEDLINE/PubMed, AMED and PsychINFO with no date limitations and searching all fields. The 2008 Cochrane Review “Interventions for alopecia areata” was also used as a reference for information up to 2008, followed by a search of the terms “alopecia areata,” “alopecia totalis” and “alopecia universalis” without any modifiers from 2007 onward for a comprehensive search of recent literature that was not covered in the Cochrane Review. Searches were also performed for these terms without modifiers on clinicaltrials.gov and the World Health Organization Clinical Trials Registry Platform (<http://apps.who.int/trialsearch>) for upcoming studies.³ The search was performed in October 2009 and a modified search again in September 2009.

TREATMENTS FOR ALOPECIA AREATA

Assessing efficacy of treatments for alopecia areata is complicated by the fact that there are few published randomized controlled trials. There are several uncontrolled trials and reports with non-ideal criteria to evaluate treatment progression and long-term follow up is not included in most of the published works. The definition of “success” varies in different studies with most but not all focused on cosmetically acceptable hair regrowth. Lastly, until recently the criteria to analyze hair regrowth and extent differ among most of the studies. The treatments that will be reviewed in this chapter are presented in Table 19-1. In 1999 and 2004, the Alopecia Areata Investigational Assessment Guidelines were published and were subsequently applied to up to 30% of new investigations providing some standardization to the description of disease extent characterization and response to therapy.^{22,23} Treatments for alopecia areata that will be reviewed in this chapter include the medications and devices noted in Table 19-1.

TOPICAL THERAPIES

Anthralin

The use of anthralin as a treatment for alopecia areata was first described in 1979, in a study in which 21 of 24 patients with patchy alopecia areata and three of eight patients with alopecia totalis developed induction of hair growth with once daily anthralin application.²⁴ It was hypothesized that the irritant contact dermatitis induced on the affected skin was the cause of hair growth. When a low concentration regimen was used on 10 patients, and was unsuccessful and no patients achieved significant hair growth, it was suggested that a higher concentration requiring induction of more irritation was necessary for a therapeutic benefit.²⁵ In a 1987 study, 68 patients with severe alopecia areata

TABLE 19-1 Treatments for Alopecia Areata

Topical

1. Anthralin
2. Calcineurin Inhibitors
 Tacrolimus
 Pimicrolimus
3. Corticosteroids
4. Minoxidil
5. Photodynamic Therapy (PDT)
6. Prostaglandin Analogues
7. Sensitizers
8. Targretin Gel
9. Topical Psoralen plus Ultraviolet Light (PUVA)
10. Narrowband Ultraviolet Light (NBUVB)

Systemic Medications

1. Corticosteroids
2. Cyclosporine
3. Minoxidil
4. PUVA
5. Sulfasalazine

Intralesional Steroids

Biologics

Devices

Combination Therapies

“Natural” Treatments

1. Aromatherapy
2. Onion Juice
3. Topical Garlic

Miscellaneous – There are Several

1. Isoprinosine, Thymopentin, Nitrogen Mustard, Azathioprine, Capsaicin, Vitamin D analog Calcipotriol, Intralesional Interferon alpha-2, Croton Oil, Sodium Lauryl Sulfate, Benzyl Benzoate, Phenol, Staphylococcus-Streptococcus vaccine, Dapsone, Griseofulvin, Topical Tretinoin, Relaxation, Acupuncture.
2. Aromatherapy
3. Cryotherapy
4. Hypnosis
5. Antidepressants

applied higher concentrations of anthralin (0.5% - 1%), and had a more positive response, with 25% of subjects achieving an acceptable cosmetic response, and 71% of responders maintaining hair growth for the duration of therapy. Adverse effects were typical of an irritant dermatitis and included erythema, scaling, and pruritus in the treated areas.²⁶

More recent studies have focused on the molecular mechanisms of action of anthralin, such as its possible immunomodulating qualities.²⁷ In 2005, a study of 31 patients with patchy alopecia areata, compared the efficacy of 0.5% topical anthralin to 20% topical azelaic acid. An overall similar efficacy rate of 53.3% of the azelaic acid group and 56.2% in the anthralin group was documented suggesting a “shared” irritant quality.²⁸ To date, no randomized controlled trials have been performed to evaluate

the efficacy of anthralin, and available study results are limited by study design and patient population size.

Calcineurin Inhibitors

Topical Tacrolimus and Pimecrolimus

Tacrolimus and pimecrolimus have been used for many years as immunosuppressant medications in organ transplantation and in T-cell mediated autoimmune diseases.²⁹ They exert anti-inflammatory and immunomodulatory activities inhibiting transcription following T-cell activation of several cytokines. Application of topical tacrolimus in rat and mouse models of alopecia areata suggested that the use of this drug could be effective in treating alopecia areata.^{30,31} There are however no randomized clinical trials using these treatments for human alopecia areata but the results of two open-label studies have provided some useful information.

In 2004, 17 patients were enrolled in a study for 30 weeks.²⁹ Tacrolimus ointment 0.1% was applied twice daily in the affected scalp for 24 weeks. After stopping the treatment, the subjects were observed for 6 weeks. Only 11 patients completed the study, six discontinued participation, two because they found the greasy ointment to be inconvenient to use. Of these 11 subjects who completed the study, only one showed hair regrowth, the others experienced no change or even further loss. The authors suggested that this lack of efficacy could be related to insufficient penetration of the current ointment formulation and the selection of the patients.

A pilot study with pimecrolimus 1% cream versus placebo including 15 patients, revealed a similar type of response as was seen with tacrolimus. Even though all the enrolled patients had alopecia areata with duration of less than 2 years, the efficacy of Pimecrolimus was no better than placebo.³²

Although there is a theoretical concern, there is no evidence to suggest an increased risk of cutaneous or visceral cancer in patients applying topical pimecrolimus or tacrolimus.³³⁻³⁵ Notably, tacrolimus is not atrophogenic and at concentrations that had efficacy similar to 0.13% clobetasol, it did not cause atrophy of the skin.³⁶

Topical Corticosteroids

A variety of topical corticoids with different potency/category and different types of vehicles are available and are frequently used to treat AA. In 1972, Kligman and Leyden tested the topical application of 2.5% dexamethasone using penetration enhancer vehicles to treat 26 patients, including patients with alopecia totalis and patchy type of alopecia areata. Group 1 (10 patients) applied the solution to one or more areas of alopecia, leaving at least one untreated as control. Sixty percent of these patients had definite signs of regrowth in 1 month. Group 2 (22 patients)

were treated first with oral prednisone (beginning at 30 mg daily and gradually reducing the dose till 0 for 5 weeks) and after the oral steroid course, the ones who showed signs of regrowth, 18 of the 22, received the topical dexamethasone formulation to apply three times a day. In 17 cases the hair growth initiated by the oral steroid was maintained by the topical application.³⁷

In a 1992 review, Fiedler et al. have reported promising clinical results using topical steroids for AA. Application of 0.05% betamethasone dipropionate cream twice daily, was shown to work well, particularly well in children, even in some with 100% hair loss. According to the investigators, at least 3 months of uninterrupted treatment was necessary to assess hair regrowth.³⁸

Pascher et al. demonstrated significant responses in patchy AA with the use of topical 0.2% fluocinolone acetonide cream. These authors reported hair regrowth in six of nine patients with alopecia totalis. The results were surprisingly different between different ages. Children younger than eleven obtained 100% regrowth, adolescents younger than 16 obtained 50% and adults only 33%.³⁹

The use of clobetasol propionate 0.05% under occlusion for 6 weeks in patients with alopecia universalis, using a half-side technique also commonly called a half head study, was associated with almost a 29% response rate. However, three patients relapsed in the 6-month follow-up period. Occurrence of hair regrowth only in the treated half of the scalp clearly showed that the efficacy of this treatment is a result of a local and not systemic effect of the drug. In the total of 28 patients, six did not conclude the study because of side effects or lack of compliance.⁴⁰

Topical 0.25% desoximetasone cream was also tested in a 12-week course and when compared to placebo showed a moderate hair regrowth response in alopecia areata patients. There was a trend toward more regrowth with the topical, but the rate of complete hair regrowth was not statistically significant when compared with placebo.⁴¹

In more recent trials, investigators focused on finding the most appropriate vehicles to use for the management of alopecia areata. Mancuso et al. in a randomized clinical trial, demonstrated that betamethasone valerate foam was effective and well tolerated by patients with mild to moderate AA. In a 12-week treatment study in which one group of patients with mild-to-moderate alopecia areata applied betamethasone valerate (BVF) cream and the other, betamethasone dipropionate lotion (BDL), a regrowth score (RGS) >3 was observed in 61% of patients in the BVF group compared to 27% in the BDL group ($P<0.03$).⁴²

The efficacy and safety of clobetasol propionate 0.05% foam to treat moderate to severe disease has also been examined. In a 12-week within patient study, (right versus left side of scalp) regrowth of at least 50% was noted seven of 34 of the treated sites compared to one of 34 on the non-treated side.⁴³

According to Fiedler, in 15 years of using topical betamethasone dipropionate twice daily, no systemic side effects

were seen even in children as young as 2 years of age and older who were receiving long-term maintenance therapies.⁴⁴ Nonetheless, careful monitoring of the growth curve in children as a marker for hypothalamic-pituitary-adrenal axis suppression is advised. Side effects at the sites of application can occur. These are considered to be in large part reversible and include folliculitis, atrophy, and hypertrichosis on the face or neck.⁴⁴

Minoxidil

This vasodilating antihypertensive drug was noted in the 1980s to have a prominent side effect of hypertrichosis. Upon this discovery, several case series and reports were described in which minoxidil was used topically for the treatment of alopecia areata with some success.⁴⁵ This led to a modified double blind crossover study, comparing 1% topical minoxidil with placebo in 30 patients with patchy alopecia areata and alopecia totalis. A cosmetically acceptable response was seen in 16 patients, none of whom experienced adverse effects. It was also noted that those patients with more extensive disease were less likely to respond.⁴⁶ In a subsequent study by Vanderveen et al. 15 patients with alopecia totalis or universalis applied either 1% or 5% topical minoxidil. None achieved hair regrowth despite blood levels similar to a group of patients with androgenic alopecia for whom the treatment was more successful.⁴⁷ Vestey et al. also found no significant difference in a prolonged double-blind trial of 1% minoxidil in hair growth of 50 patients with extensive alopecia areata.⁴⁸

A larger study evaluating a 1% topical solution on 24 patients with patchy alopecia areata and 24 patients with alopecia totalis or universalis was more promising. Twenty five patients saw terminal hair growth, and of those, 11 saw cosmetically acceptable results. Hair growth in this study was not associated with disease severity or extent, and began approximately 2 months after treatment was started. Notably, no systemic side effects were found.⁴⁹ Similarly, in a study of 54 patients, 7 with alopecia totalis and 47 with patchy disease, 28 patients applied topical minoxidil and 26 patients received a placebo formulation, 50% of the treated group achieved cosmetically acceptable regrowth.⁵⁰ However, these results were again contradicted by a double-blind crossover trial of 15 patients with alopecia totalis studying 3% topical minoxidil versus placebo. After 16 weeks, the results showed no cosmetically acceptable hair regrowth in patients with extensive well-established alopecia totalis. The results showed only some vellus hair growth which was not deemed cosmetically acceptable.⁵¹ These inconsistent conclusions continued in a 3-month double-blind crossover study of 1% topical minoxidil on 23 patients with extensive alopecia areata, 13 of whom showed an increase in terminal hair growth, but only one achieved a cosmetically acceptable result.⁵²

To further examine the effectiveness of minoxidil, a study was completed evaluating 5% minoxidil solution in

47 patients with severe alopecia areata. Notably, 85% of patients had terminal hair regrowth after 48-60 weeks of treatment. Although for most of these subjects, the hair growth was not cosmetically acceptable, these results were significantly better than with a 1% solution.⁵³ Furthermore, a study of 66 patients also with extensive scalp hair loss resulted in terminal hair growth in 38% of patients with 1% solution and 81% of patients who applied a 5% solution. An observation from this study was that occlusion of the area must be maintained for optimal results. It was also noted that recurrence of hair loss was frequent upon cessation of treatment.⁵⁴

Multiple other studies have shown modest, if not dramatic benefits that minoxidil may have in the treatment of alopecia areata. A 3% solution has also been studied. One double-blind evaluation of 30 patients with extensive alopecia areata who applied either 3% minoxidil twice a day for 64 weeks or placebo for 12 weeks followed by 3% minoxidil, the remainder of the weeks showed no statistically significant difference at 12 weeks. At 64 weeks, 45% showed a cosmetically acceptable result but none of those patients had 100% hair loss at baseline. Hypertrichosis of the face was noted as an adverse experience in five of the subjects.⁵⁵⁻⁵⁶ In another double-blinded, placebo controlled trial of 1 year's duration, patients with extensive disease who applied 3% topical minoxidil did achieve better hair growth, but only three of the 11 minoxidil-treated patients achieved a cosmetically acceptable result. In this study, there were no significant adverse experiences.⁵⁵ A randomized, double-blind, controlled study of 21 patients with alopecia totalis or universalis using 3% topical minoxidil was unimpressive; no significant cosmetically acceptable results were achieved, although transient regrowth of vellus hair was present in eight patients. Long-term efficacy over 3 years showed maintenance of results but no additional cosmetically acceptable growth in those who did not show it initially, and none of the patients went into complete remission during treatment.⁵⁷⁻⁵⁸

Photodynamic Therapy (PDT)

Photodynamic therapy involves the administration of a photosensitizer, followed by its activation with light to generate a therapeutic effect. 5-Aminolevulinic acid (ALA) is a photosensitizer precursor that is transformed by cells into protoporphyrin IX (PpIX), which can in turn be activated by red light.⁵⁹ The knowledge that ALA is primarily metabolized to PpIX in activated lymphocytes, and that this photosensitizer has been shown to induce apoptosis in cell culture and tumors, created a reasonable link to explore the role of PDT in AA.⁶⁰⁻⁶²

In 1987, Da Monfrecola et al. reported hair regrowth in patients with alopecia areata after PDT using a topical formulation of the photosensitizer haematoporphyrin.⁶³ Despite the interesting possible link between this therapeutic approach and alopecia areata, only one randomized

clinical trial is available for review. Bissonnette et al. investigated the effect of PDT in AA, trying to clarify the “theoretical hypothesis” that ALA-PDT could improve AA by inducing apoptosis around the hair follicles. In a group of six patients, ALA lotion at 5%, 10% and 20% as well as the vehicle alone were applied separately to different areas of the scalp—followed 3 hours later by exposure to red light at each treatment session. A significant increase in erythema and pigmentation was observed in the concentrations used, suggesting that PpIX was being activated. With fluorescence microscopy, bright red fluorescence was seen only in the epidermis and sebaceous glands, and was not seen around the hair follicles and after 20 twice-weekly treatment sessions, no significant hair regrowth difference between the vehicle and the three ALA-treated sites was observed. It was thus concluded that the use of PDT was ineffective in the treatment of alopecia areata.⁵⁹ Nevertheless the authors had some considerations related to factors that could be implicated in the final results. They suggested that number of treatments, number of patients, length of period between drug application and light exposure and low level of the PpIX synthesized (not enough to be detected) could be explanations to explain the negative findings. The use of oral ALA was discussed as a future perspective to overcome the obstacles because Divaris et al. showed phototoxic damage to hair follicles and sebaceous glands after systemic use of ALA.⁶³

Prostaglandin Analogues

Prostaglandins and specifically Prostaglandin F2 alpha analogs bind to cell surface receptors activating phospholipase C. This enzyme orchestrates a variety of responses in cells such as stimulating gene expression and division. Latanoprost and bimatoprost are phenyl substitute analogues of prostaglandin F2 alpha, and are widely used in an ophthalmic solution to lower intraocular pressure in glaucoma.

In 1997, the first data relating eyelash regrowth to this type of drug was published. A retrospective trial done by Johnstone et al. reported that in 43 patients receiving latanoprost monocularly, hypertrichoses of eyelashes occurred in all of the eyes treated, using the contralateral eye as a control.⁶⁴ After this work some case reports were seen reinforcing this relationship but none were related to patients with alopecia areata.⁶⁵

In 2002, a macaque model was used to elucidate the effect of latanoprost for hair regrowth using animals with androgenetic alopecia. Latanoprost was applied topically using 50 ug/mL and 500 ug/mL compared to placebo. The smaller concentration caused minimal hair regrowth while 500 ug/mL induced moderate to marked hair regrowth with 5-10% conversion of vellus hairs to intermediate or terminal hairs.⁶⁶

After several additional studies, a case report of an 11-year old girl with bilateral loss of eyelashes assumed

to be related to alopecia areata was published. She was prescribed Latanoprost and demonstrated pronounced lash growth of eyelashes on all four lids after 8 weeks of use.⁶⁷

Ross et al., were one of the first to publish a study of prostaglandin analogues for alopecia areata. This was a 16-week randomized, right-left, investigator blinded study in adults with severe eyebrow AA. The randomly assigned subjects treated one eyebrow with topical latanoprost (3 mcg) for 12 hours daily over 12 weeks. In a total of eight patients, seven did not show any regrowth. One patient did have a positive result; however, it was bilateral and was most likely the result of administration of prednisone therapy during the treatment period.⁶⁸

In 2008, another trial to assess the effect of cutaneous application of latanoprost for alopecia areata was published. Bimatoprost was also tested and both drugs were used in the same concentration as they are used for glaucoma. The drugs were applied directly to the affected eyelid margins of patients with alopecia areata. None of the patients presented appreciable regrowth. It was concluded that the method of drug delivery was yet to be elucidated.⁶⁹

One year later the use of topical latanoprost was again assessed, but at this time in the eyebrows and eyelashes. In 26 patients, only one showed partial regrowth.⁷⁰

Instilled bimatoprost ophthalmic solution was also explored in an open label prospective study to evaluate eyelash regrowth in alopecia areata patients. No appreciable regrowth was seen in patients with 95% to 100% eyelash loss at baseline. Patients with up to 30% and 40% eyelashes present at baseline did experience additional eyelash growth, suggesting that patients with less extensive eyelash loss may benefit from this therapeutic option.⁷¹

Sensitizers

Three different topical sensitizers have been used to treat alopecia areata with some evidence of efficacy. These three include dinitrochlorobenzene (DNCB), diphenycyprone (DPCP), and squaric acid dibutyl ester (SADBE). The theory of immunomodulation was proposed by Happle et al. in 1986, when he showed that skin treated with topical sensitizers showed changes in the peribulbar CD4/CD8 lymphocyte ratio.⁷² In 2006, Herbst et al. reinforced and complemented the theory providing evidence that long-term treatment with a contact sensitizer, allows for the recovery of the hair follicle by driving autoreactive T cells into activation-induced cell death.⁷³

DNCB was first used for alopecia areata in 1976, but because of concerns over the mutagenic properties of the drug in *Salmonella enteritidis* serotype Typhimurium and its absorption through the skin with ultimate excretion in urine, its use has in large part been discontinued.⁷⁴ Because SADBE is stated to be relatively unstable in acetone solution, DPCP is the most commonly used sensitizer in clinical practice.⁷⁵⁻⁷⁶ Happle et al. enthusiastically introduced the use of DPCP for the treatment of alopecia areata when

they reported that 67% of treated patients had a satisfactory response to this treatment.⁷⁵ In a larger study of 139 patients completed by the same investigator, a response rate of 50.4% was subsequently reported.⁷⁷ However, some years later a review of 17 reported cases series concluded that though 50-60% of patients may achieve a response to DPCP, the range of reported responses was very wide, between 9 to 87%.⁷⁸ In a follow-up study, Gordon et al. included a total of 32 patients and demonstrated that only nine patients maintained regrowth without further DPCP treatment for an average of 19.8 months, while nine had poor regrowth with continued use of the drug and 5 discontinued the treatment.⁷⁹

Micali et al. studied the use of SADBE for alopecia areata and demonstrated an 80% rate of regrowth in less severe forms and 49% in more severe cases. The failure rate was found to be higher in patients with the more severe form (29%), compared to a 7% rate only for patients with mild AA.⁸⁰ The same investigator later studied 54 patients with extensive alopecia areata treated with SADBE. Data collected were compared with those of a matched control group of 54 patients who did not receive any treatment. At the end of therapy, the treatment group showed a statistically significant ($p<0.001$) improvement. At follow-up, there was no significant change in the previous relapse rate (treated 44% vs. control 52%).⁸¹

A review of AA treatments in 2003 presented the evaluation of the 17 most significant controlled trials from 1983 to 2001, using DPCP and SABDE studies to test the efficacy of treating AA. The response rate of treatments represented by cosmetically acceptable hair regrowth varied from 29% to 78%. The investigators suggested that these differences could be explained by the different extent and durations of alopecia areata present in the patient populations prior to the treatment in each study and by the different treatment methodologies.⁸² In yet another retrospective chart review of patients from 1996 to 1999, 33% were found to attain cosmetically acceptable or total regrowth with topically applied SADBE.⁸³

An Indian study in 2006 involved 70 patients treated with SADBE for 4 months. The overall success rate was 43%. For subjects with <50% of scalp involvement the rate was 68%, however for those with > 50% involvement the success rate was 29%. Additionally 81% of the responders (21 in 26) had relapse occurrence.⁸⁴

In a study completed in Greece, 64 patients with alopecia areata were sensitized with 2% DPCP and treated with graduated concentrations adjusted to maintain erythema and pruritus on the scalp for 48 hours. The follow up was 2 years. A total of 83.3% of the subjects responded to therapy, although a significant difference in responses was noted and varied between regrowth of vellus hair, sparse pigmented terminal hairs, and terminal hairs in patches of alopecia, as well as regrowth of terminal hair on the entire scalp. Relapses were noted to occur in approximately 70% of the patients.⁸⁵

The side effects of topical immunotherapy need to be considered. Although the desired reactions inherent to the treatment include a mild dermatitis, undesired side effects are noted in 2-5% of patients and include vesicular and bullous reactions at the initiation of treatment before appropriate individual concentrations are determined, dissemination of allergic contact dermatitis, urticaria or erythema multiforme-like reactions, and pigmentary disturbances such as postinflammatory hyperpigmentation. Notably, no long-term side effects have been reported after 18 years use of DCPC and 21 years of SADBE treatments worldwide.⁸²

Targretin Gel

In 2009, a phase I/II randomized bilateral half-head comparison study was performed to evaluate the efficacy of bexarotene gel for alopecia areata. Bexarotene is a synthetic retinoid that target the retinoic acid X receptor, which has been shown to have immunomodulatory effects beneficial in cutaneous T-cell lymphoma. In this study, 42 patients were included, 34 with patchy disease, 3 with alopecia totallis, and 5 with alopecia universalis. One percent bexarotene gel was applied topically to half of the head twice daily for 6 months; 12% achieved 50% or greater regrowth on the treated side, and an additional 14% achieved similar results bilaterally. This study, like many others, was limited by an inability to differentiate drug-induced and spontaneous growth, but the results suggests that bexarotene is a well-tolerated treatment that warrants further study.⁸⁶

Topical Psoralen plus Ultraviolet A Light (PUVA)

The use of psoralens and ultraviolet A light (PUVA) for alopecia areata is based on the concept that PUVA therapy may influence the inflammatory infiltrate that surrounds affected hair follicles. There are many uncontrolled studies of both oral and topical PUVA for alopecia areata. Both oral and topical have been tried. In this section, results of topical studies will be emphasized.

Weissman et al. were the first to report encouraging results from the use of topical methoxsalen and UVA radiation of the scalp. The range of hair regrowth in this study varied from 15% to 90% in a small group of five patients.⁸⁷ Lassus et al. subsequently reported on 41 patients who were treated with topical or oral methoxypsonalalen and UVA. They reported good to excellent results in 73% of patients.⁸⁸

Claudy et al. reported treatment failure to local UVA radiation and topical methoxsalen but positive results for oral methoxsalen and total skin surface irradiation in two consecutive studies in 1980 and 1983.⁸⁹ In a small group of patients treated with oral methoxsalen and total skin surface irradiation, 64.7% of the patients had a complete

or more than 90% regrowth. During a follow-up period of 18.6 months, three patients experienced a relapse.

Mitchell et al. in a study of 22 patients demonstrated almost a 46% positive response to treatment with topical methoxysoralen and UVA in which 36% had excellent hair regrowth and 9% had good regrowth. In a follow-up mean period of 8.3 months, 8 of 9 responders experienced a relapse, with the investigators concluding that this approach does not change the long-term course of AA.⁹⁰ In two retrospective reviews of clinical experience the response rate was also found to be low (6.3-13.1% after at least 3 months treatment) and according to the investigators, no better than spontaneous improvement.⁹¹⁻⁹²

In a 2005 report of 149 patients, 124 patients with alopecia areata and 25 patients with alopecia totalis/universalis treated with topical 8-methoxysoralen and UVA were reported to have different treatment responses. Of the alopecia areata totalis/universalis patients, 44% showed only vellus hair regrowth and 56% had good (>50% scalp hair regrowth) and excellent results (>80% scalp hair regrowth). Three patients experienced relapses in the follow-up period. In contrast, patients with patchy alopecia, 85% demonstrated good or excellent hair regrowth; 11% had fine white hair regrowth and 4% no response.⁹³

Psoralen-UVA-Turban is a modification of PUVA bath therapy in which a dilute Psoralen solution is administered selectively to the scalp of patients. Twenty patients were treated with 8-methoxysoralen at a dilution of 0.0001% (1 mg/mL), applied for 20 minutes to the scalp followed by UVA radiation. Treatments were performed 2 or 3 times a week. Hair regrowth was observed in 15 patients, a 75% of overall success rate. Six patients experienced total regrowth (4 with patchy disease and 2 with alopecia totalis/universalis). Nine patients (5 with patchy disease and 4 with alopecia totalis/universalis) or 45 % had partial regrowth. Five patients did not respond to this treatment. Analyses on the different responses according to the type of alopecia areata revealed that 100% of patient with patchy disease achieved some kind of regrowth while only 55% of the patients with alopecia totalis/universalis did. The conclusion was that this treatment was effective, particularly for patchy alopecia areata.⁹⁴⁻⁹⁵ In general, regrowth is usually detected after 20-40 sessions, with the maximum effect developing within 1 year.⁹⁶

Narrowband Ultraviolet Light (NBUVB)

Despite positive results with other autoimmune diseases such as psoriasis, the use of UVB phototherapy for alopecia areata has been only minimally studied. This therapy was first described in 1961, when a Kromayer lamp was used to treat 32 patients with extensive alopecia areata weekly or every other week. Twenty five patients achieved hair regrowth within 3 months, and full regrowth occurred in 14 of the 25, however, several reported relapse upon discontinuation of treatment.⁹⁷ A later evaluation of

multiple dermatoses including eight patients with alopecia areata used a novel monochromatic excimer light (MEL) light delivery system and resulted in 4 individuals achieving complete hair regrowth with a mean of 5.1 well-tolerated sessions.⁹⁸ However, an additional study which included eight children with alopecia areata, narrowband UVB phototherapy failed to produce results in any of the subjects, perhaps due to different delivery methods or the age of the patients.⁹⁹

SYSTEMIC THERAPIES

Corticosteroids

Since interest in the responsiveness of alopecia areata to systemic corticosteroids began in the 1950s, (Dillaha, Shelley) there have been many investigations done to examine the safety and efficacy of this therapy, as well as appropriate dosing regimens.¹⁰⁰⁻¹⁰¹ Numerous small studies on the effectiveness of systemic steroids administered orally or intramuscularly and long treatment periods led to enthusiastic publications.¹⁰²⁻¹⁰³ Later it was suggested that extensive disease is not as amenable to treatment as less extensive disease and the detrimental effects of prolonged systemic therapy including striae and truncal obesity, among others, in addition to the likelihood of disease recurrence, upon discontinuation of therapy led to less enthusiasm for this approach.¹⁰²⁻¹⁰³

Interest then grew for pulse dosing as a way to minimize adverse effects. Preliminary trials of various regimens obtained similar results, showing that such dosing had the capability of temporarily arresting and possibly putting into remission active alopecia areata, especially patchy multifocal disease. The treatments appeared to be well tolerated and safe. However, those with prolonged disease duration or extensive distribution seemed to respond to a lesser degree to this therapy than those with recent onset (<12 months). Recurrence of hair loss occurred in many patients with this dosing regimen as well.¹⁰⁴⁻¹⁰⁸ Similar results were found in children treated with pulse therapy.¹⁰⁹⁻¹¹⁰

In an open study of 45 patients, IV pulse of 250 mg methylprednisolone was administered twice a day for three consecutive days to patients at 1, 3, 6, and 12 months. All patients had disease duration of less than a year, the extent of which varied. Twenty patients had patchy disease, 10 ophiasis pattern hair loss, 6 alopecia totalis and 9 alopecia universalis. This treatment stopped hair loss in half the patients and lasted at least 12 months in 54% of responders. Minimal side effects were experienced, and patients with multifocal alopecia areata experienced the greatest benefit while those with ophiasis and universalis patterns obtained a less pronounced improvement.¹¹¹

The first randomized, placebo-controlled study published in 2005 included 43 patients with extensive disease who received either a placebo control or 200 mg of oral prednisolone weekly for 3 months. Patients were

followed monthly for 3 months subsequent to completion of the study. None of the treated patients had been diagnosed with the disease for greater than 2 years. Of the 23 patients in the treated group, eight experienced significant regrowth while none of the patients in the untreated group did. However, two of the patients who achieved regrowth experienced a relapse during the follow-up period. The results of this study supported a role for systemic corticosteroids, particularly pulse dosage, in the treatment of alopecia areata.¹¹²

The question of which systemic regimen is most effective with the fewest side effects in both limited and extensive disease was addressed by Kurosawa et al.¹¹³ Fifty-one patients with patchy disease and 38 patients with alopecia totalis/universalis were randomly divided to receive either pulse therapy, low-dose daily dexamethasone, or monthly intramuscular injections. The response rate and relapse rates were significantly better in the pulse therapy and intramuscular steroid groups, however 23% of those receiving intramuscular steroid injections and 7% of those who received pulse therapy were observed to have temporary impairment of adrenocortical function.

To confirm these findings, Nakajima et al. studied a larger population of 139 patients with severe disease, 90% with disease duration of less than 1 year, and 72.7% with hair loss affecting >50% of the scalp.¹¹⁴ Among the group with a disease onset of <6 months, 59% had a response rate of 75% or greater while only approximately 16% of patients with a longer duration since disease onset had a similar response. Furthermore, among the recent onset patients, those with <50% hair loss had a response rate of 88%, while those with 100% hair loss only responded in 21% of cases. These results reaffirmed the variable success rates of this treatment with different types of alopecia areata.

Overall, the evidence suggests that systemic therapy with corticosteroids is an important part of the management of active disease, especially in specific groups of patients. The risks and benefits of this treatment must however be weighed individually for each patient as there are significant side affects associated with systemic steroid therapy and relapses are likely. Furthermore, long-term outcome studies remain to be completed.¹¹⁵

Cyclosporine

Several case reports have been published on the effectiveness of systemic and topical cyclosporine.^{116,117} In one of the first studies, six patients received oral cyclosporine (two with patchy alopecia areata, two with alopecia totalis, and one with alopecia universalis). Scalp hair regrowth was seen in all subjects by the fourth week. Cosmetically acceptable regrowth was experienced in three of the six patients; however, all experienced a relapse within 3 months of discontinuation of therapy.¹¹⁸ In a slightly larger study of fifteen patients who received oral cyclosporine for 6-12

months (eight with alopecia universalis, two with alopecia totalis, and five with patchy alopecia areata), twelve experienced vellus hair growth. Of those, seven went on to develop terminal hair after 3-8 months; two patients experienced full hair regrowth. Side effects were minimal except for one patient who withdrew from the study because of hypertension and another who experienced gingival hyperplasia. Unlike corticosteroids, responsiveness to therapy did not appear to correlate to type or severity of disease.¹¹⁹

Interest in the topical application of cyclosporine also evolved, however a study by Gilhar et al. showed no beneficial response in any of 10 patients with alopecia areata and alopecia universalis who used a topical formulation of cyclosporine A in an oil preparation for 12 months.¹²⁰ A placebo-controlled study of 43 patients revealed development of terminal hairs in a group receiving topical cyclosporine, but no patient experienced complete scalp hair regrowth. Side effects were minimal, with occasional itching or irritation and no evident laboratory abnormalities.¹²¹

These findings provide encouraging data to support the further study of cyclosporine in randomized, controlled, large studies to fully evaluate the efficacy and safety of this treatment. Future studies could also focus on a preferred dosage and delivery system.

Minoxidil

Because minoxidil is limited by its cutaneous solubility and absorption, the efficacy of employing an oral route was evaluated in a 1987 study of 65 patients with extensive, treatment-resistant alopecia areata.¹²² Despite a more rapid and extensive response, only 18% patients obtained a cosmetically acceptable response. It was concluded that oral minoxidil was unlikely to be effective as a single agent in the treatment of severe disease. Specifically, a total of 65 patients were entered into a study to determine the safety and efficacy of low-dose (5 mg every 12 hours) oral minoxidil in the treatment of severe AA. Patients included were 27 men and 38 women, ranging in age from 13 to 55 years (mean, 31 years). Extent of scalp hair loss at baseline was 75% to 100% in 44 (68%) patients, 25% to 74% in 19 (29%), and 0% to 24% in two (3%). Thirty-four patients of the 65, were treated in a previous study with topical 5% minoxidil. They had experienced either no response to treatment or no additional response in the preceding 3 to 6 months. These patients were subsequently enrolled in this same study with oral minoxidil. Cosmetic response was defined as sufficient terminal hair regrowth so that the patient no longer needed a wig or cap to conceal any residual alopecia. Fair response was defined as extensive, but not cosmetic, regrowth. Slight response was defined as sparse terminal hair regrowth. Nonresponse was defined as vellus or no regrowth. Scalp biopsies were performed at baseline and at 6 months. Serum minoxidil levels were monitored at each

visit for the first 12 to 18 months of treatment. Strict adherence to a 2-g sodium diet was required for the duration of treatment. The mean duration of treatment was 53 weeks (range, 20 to 115 weeks).

Response to oral minoxidil was seen in 52 (80%) of the 65 patients, in 21 (100%) of 21 patients with baseline scalp hair loss less than 75%, and in 31 (70%) of 44 patients with baseline scalp hair loss greater than or equal to 75%. Cosmetic response was seen in 12 (18%) of the 65 patients, in eight (38%) of 21 patients with less than 75% scalp hair loss, and in four (9%) of 44 patients with greater than or equal to 75% scalp hair loss. Cosmetic regrowth was maintained during treatment in all 12 patients, although minor episodes of hair loss occurred in some. Serum and tissue levels showed no correlation with each other or with response to treatment. Thirty-three patients discontinued taking oral minoxidil, 19 because of lack of efficacy, and 14 for personal reasons. Seven of these patients reported onset of hair loss within 2 to 8 weeks after discontinuation of treatment.

Oral minoxidil and topical 5% minoxidil produced similar percentages of responders. The mean time to regrowth was similar in both studies. Comparison of the 34 patients who were treated in both studies showed that hair regrowth progressed more rapidly and was more extensive with oral than with topical 5% minoxidil. Cosmetic response was enhanced with oral minoxidil (12/65 [18%]) vs topical 5% minoxidil (6/47 [13%]). The mean time to a cosmetic response was also shortened with oral (34.8 weeks [range, 12 to 61 weeks]) vs topical 5% minoxidil (62 weeks [range, 16 to 158 weeks]).

Oral minoxidil at the dose studied was relatively well tolerated and was used in an attempt to bypass the barrier to percutaneous absorption and the limitations of minoxidil solubility. Although efficacy was enhanced, only 18% of the patients achieved a cosmetically meaningful response. Mean tissue levels of minoxidil were similar for fair and cosmetic responders versus slight and nonresponders. These data suggest that even if topical minoxidil preparations are improved such that absorption and solubility limitations are overcome, minoxidil as a single therapeutic agent is expected to be cosmetically effective only in a minority of patients with severe AA.¹²³

PUVA

As noted previously, the use of Psoralens and UVA (PUVA) for AA is based on the concept that the PUVA therapy may eradicate the inflammatory infiltrate that surround the affected hair follicles. In 1980, a group reported 41 patients who were treated with either topical or oral methoxsalen and UVA. Good to excellent results were obtained in 73% of their patients.¹²⁶ Claudio et al. reported treatment failure to local UVA radiation and topical methoxsalen and positive results for oral methoxsalen and total skin surface

irradiation. For oral methoxsalen and total skin surface irradiation, 64.7% of the patients had a complete or more than 90% regrowth in a small group of 17 subjects total. In a follow-up mean of 18.6 months, three patients relapsed.¹²⁴

Several relevant features of PUVA need be considered before choosing this therapeutic approach. Systemic PUVA can induce nausea, vomiting, possible burning of the scalp, pigmentary alterations, photo aging, squamous cell carcinoma, and photosensitization of the cornea and the entire skin. Local PUVA or PUVA-bath can avoid the systemic effects as systemic burden of 8-MOP and the duration of photosensitivity in the skin is shorter following local application, but the available epidemiologic data do not support conclusions that PUVA-bath per se is less carcinogenic than oral PUVA therapy. All forms of PUVA therapy with 8-MOP irrespective of the route of administration of Psoralen, are expected to contribute to a small, dose-dependent increase in non-melanoma skin cancers.¹²⁵

Sulfasalazine

Sulfasalazine was developed in 1938 for the treatment of rheumatoid arthritis. Its anti-inflammatory drug composed of sulfonamide and salicylate.¹²⁶ This drug promotes inhibition of the chemotaxis of inflammatory cells and the production of antibodies, acting as an immunosuppressive and immunomodulatory agent.

Ellis et al. were the first group to report the use of sulfasalazine for AA. They reported 23% of cosmetically acceptable hair regrowth in a group of 30 patients. The results, however, were in large part anecdotal.¹²⁷

In 2007, an isolated case report showed one patient who showed 50% hair and eyelash regrowth after 7 months on sulfasalazine on progressive doses from 1 to 3 mg daily. The patient however had to terminate the treatment because of adverse events such as dizziness and headache. All fibers including eyelashes were shed within a few months after discontinuing the medication.¹²⁸

Thirty-nine AA patients with persistent (recalcitrant to other therapies) disease were treated with 3g of sulfasalazine for 6 months and evaluated using the SALT score in a prospective trial. A good response occurred in 25.6 %, moderate response in 30.7% and poor or no response in 43.5% of the patients. Recurrence was observed in 12.8% of the responders (3 with moderate and 2 with good response). 5.1% of the patients experienced dizziness and headaches and 20% dyspepsia.¹²⁹

An open label uncontrolled trial in 2008 included 22 AA subjects with recalcitrant or severe AA on a regimen of 1 mg to 3 mg daily. The treatment duration ranged from 6 to 24 months. Overall rate response achieved 68.2%. 27.3% of the patients experienced complete hair regrowth, 40.9% partial hair regrowth and 31.8% no hair regrowth. Side effects were observed in 31.8% of the subjects, and

included gastrointestinal distress, rash, laboratory abnormalities, and headache.¹³⁰

Combination therapy with sulfasalazine and systemic corticosteroids has been reported to be successful. A series of six case reports demonstrated the efficacy of using sulfasalazine 1 to 3 g/day along with oral methyl prednisolone 1 mg/kg/day for 3 months. After this period, complete recovery was seen and the corticosteroid was tapered. After an additional 7 months of therapy with sulfasalazine alone, patients were followed for another 16 months, maintaining full scalp hair growth.¹³¹

INTRALESIONAL CORTICOSTEROIDS

Local injection of corticosteroids into lesions of alopecia areata has been the preferred treatment since the late 1950s after this approach was described in several German and Spanish studies.¹³²⁻¹³⁶ This method theoretically provides increased delivery of an anti-inflammatory medication drug directly to the affected area while minimizing systemic corticosteroid side effects. In a smaller study comparing the effectiveness of intralesional triamcinolone hexacetonide in 11 patients to triamcinolone acetonide in 17 patients, results were encouraging, showing a majority of patients in both groups responding with a linear rate of hair growth for at least 9 months after the injection.¹³⁷ These results were reaffirmed by a larger study in 1973 of 84 patients treated with intralesional injections of triamcinolone acetonide, in which 71% of patients with patchy alopecia areata patients and 28% with alopecia totalis maintained hair regrowth at 12 weeks. Side effects from this treatment included atrophy at injection sites, which in the previously described study resolved without further sequelae in the months subsequent to treatment. The treatment was well tolerated by patients.¹³⁸ In a study of 62 patients in Saudi Arabia who received 1 monthly intralesional injection of triamcinolone acetonide complete regrowth was noted in 63% of patients at 4 months. Results revealed an increased likelihood of success in younger patients with fewer, smaller, and newer lesions.¹³⁹ In a study of 58 patients, it was suggested that the application of topical tretinoin in combination with intralesional corticosteroids had an additional positive effect on hair growth compared to the use of intralesional corticosteroids alone.¹⁴⁰

BIOLOGICS

Biologics reported to date to have some type of effect in AA are Etanercept, Infliximab, Alefacept, Adalimumab, and Efalizumab. Etanercept (Enbrel, Amgen, Inc) is a soluble TNF receptor that works by binding circulating TNF. The administration is a subcutaneous injection. Infliximab (Remicade, Centocor, Inc) is an intravenous anti TNF antibody that kills cells having surface TNF. Efalizumab (Raptiva, Genentech) is an anti -CD11a that works by inhibition the interaction by T cells and antigen presenting cells

as well as by inhibition of T cell migration from blood. This biologic though tested for the treatment of alopecia areata has since been recalled and is not available.

Alefacept (Amevive, Biogen Inc, Cambridge, MA) was designed to bind CD2, inhibit antigen presenting cell interaction with T cells and selectively reduce CD45RO+ cells. It can be administered intravenously or intramuscularly.¹⁴¹ Adalimumab is a fully humanized anti TNF-alpha monoclonal antibody

Despite the hopes for a role of biologics in the treatment of AA in 2005, a case report revealed for the first time recurrence of alopecia areata in a man with history of previous AA and rheumatoid arthritis while being treated with Etanercept for more than 2 years.¹⁴² Later additional case reports appeared describing patients developing alopecia areata while receiving biologic therapy.¹⁴³

Strober et al. studied the safety and efficacy of Etanercept in a prospective open label study in the treatment of moderate to severe AA. Seventeen patients were enrolled and they received the maximum dose of the drug approved by the Food and Drug Administration. After between 8 to 24 weeks of treatment with 50 mg subcutaneously twice a week, none of the participants showed significant hair regrowth, suggesting lack of efficacy with this approach.¹⁴⁴

In 2006 Tosti et al. additional cases of alopecia areata occurring during treatment with biologics. In one case, AA occurred during a course of Infliximab therapy in a patient with no previous history of AA. In a second case report, during a course of therapy with Efalizumab in a patient with previous patchy type disease the patient developed an extensive and refractory AA after the treatment.¹⁴⁵ In contrast, Hefferman et al. described improvement in four patients after Alefacept therapy and in a case report in 2008, complete regrowth of scalp and body hair after a single 12-week treatment course with Alefacept in a patient with Universalis type of AA was reported.¹⁴⁶⁻¹⁴⁷

In 2006, a single successful case of monotherapy treatment with Efalizumab for Universalis type of AA was published. 90% of hair regrowth was achieved after 6 months of treatment. Regrowth of body hair was slower but significant. Of note, during this period the patient's Hashimoto's thyroiditis was also treated with levothyroxine.¹⁴⁸

In 2008 the first randomized, double blind, placebo-controlled multi-center study for AA was performed with a biologic. The safety and efficacy of Efalizumab in the treatment of AA was assessed. Sixty-two patients were enrolled in a 12-week period treatment. Unfortunately, a response rate response of 8% was observed for both Efalizumab and placebo treated groups.¹⁴⁹

DEVICES/LASERS

No randomized controlled trials were found that addressed laser therapy for AA, however some reports and clinical trials are available for evaluation. Gundogan et al. were the first to reveal positive effects of a 308 nm xenon chloride

excimer laser for AA. The investigators reported that in two cases of patchy AA, after 11 and 12 sessions and within a 9 and 11-week period, there was excellent regrowth with no relapse in a follow-up period of 5 and 18 months.¹⁵⁰ It was postulated that the laser acted on the inflammatory peribulbar infiltrate perhaps through a T cell apoptotic effect.¹⁵¹

In 2004 a study involving nine patients, five with patchy AA and four with totalis or universalis, reinforced this hypothesis. Using the same type of device, lesions were treated for a maximum of 24 sessions with initial fluencies of 50mJ/cm² increased from 50 mJ/cm² every two sessions. Each treated lesion had an untreated lesion as a control. All patients with patchy disease developed moderate to excellent hair regrowth while no hair regrowth was observed in the patients with alopecia totalis or universalis. Side effects were limited to mild erythema and hyperpigmentation.¹⁵²

Another type of laser device has also been reported to be successful in alopecia areata. In one study with 16 patients, 34 resistant patches of AA were treated to assess the effect of the pulsed infrared diode laser (904 nm). It was used in 4 sessions, once a week. Regrowth was seen in 94% of the patches, with the majority of fibers expressing a normal color.¹⁵³ It was suggested that this type of laser improved microvascular circulation and reduced inflammation.¹⁵⁴ Even without exactly understanding the mechanism of action, it was suggested that this device might either alter the cellular membrane or change the previously exposed "hidden antigen".

Al-Mutairi in two consecutive trials tested the effect of 308-nm excimer laser for AA. In the first study 18 adults, AA subjects with patchy disease were treated. Regrowth was observed in 41.5% of patches. Most of lesions that responded were on the scalp, lesions on the extremities were not that responsive. All the lesions on the scalp that did not respond were in patients with bronchial asthma. In the second trial 9 children with patchy AA, as well two with alopecia totalis were treated. Regrowth was observed in 60% of the patches on scalp, while there was no notable response in the control patches and in lesions on the extremities. Reinforcing the previous observation, the four scalp lesions that did not show any regrowth were in patients with bronchial asthma. Four patients had relapse after 6 months post laser therapy. In general, in both studies the therapy was well tolerated.^{155,156}

More recently fractional photothermolysis laser therapy has been proposed to be beneficial to patients with alopecia areata.¹⁵⁷ This type of device produces a thermal damage called "microthermal treatment zones" (MZT) and characteristically spares the tissue surrounding each MZT. The stratum corneum is kept intact and there are "fractional" microscopic thermal columns, which are associated with wound healing. One single report of a patient with patchy disease treated with this device weekly for 24 weeks demonstrated that the patient could achieve complete hair regrowth in all lesions after 6 months of therapy. No relapse

was observed in 6 months follow up. The authors suggested that the mechanism of action was T cell apoptosis possibly associated to a decrease in the perifollicular lymphocyte infiltration.¹⁵⁸

COMBINATION THERAPIES

The success of systemic corticosteroids in managing alopecia areata increased interest in the idea of other therapies having an additional or synergistic effect when used in combination. In 1992, a randomized, controlled study of a 6-week prednisone taper with or without 2% topical minoxidil revealed that six out of seven combination treated responders were able to maintain hair growth versus one of six vehicle-treated responders. In a similar open trial, over 50% of patients using topical minoxidil were able to maintain hair growth at 6 months.¹⁵⁹

The combination of cyclosporine, an immunomodulator, and corticosteroids has also been studied. A small study of eight patients showed that only 25% responded to cyclosporine with low dose prednisone and several experienced severe side effects including edema, hypertension, abnormal liver function tests, and abnormal lipid levels.¹⁶⁰ However, the use of methylprednisolone pulse therapy with oral cyclosporine in another limited study showed promising results; three out of six patients with alopecia totalis and three out of 12 of patients with alopecia universalis showed hair regrowth on at least 70% of the affected area with no significant relapses after at least nine months of followup. Furthermore, side effects were minimal (mild acne, mild increase in blood pressure, etc.) and the treatment was well tolerated.¹⁶¹ One larger, but also uncontrolled study was similarly encouraging, with 38 of 43 patients with severe alopecia areata experiencing significant hair regrowth. However, nine of the responders relapsed during the followup period of 12 months, and three of the original 46 patients discontinued the study due to intolerable adverse effects. Over half of the patients in the study experienced some form of adverse effects, most commonly gastrointestinal disturbance, edema, acne, and weight gain.¹⁶²

Another agent evaluated in combination with corticosteroids for the treatment of alopecia areata is methotrexate. One retrospective study showed that 11 of 16 patients with alopecia totalis or universalis treated with combination therapy (as opposed to 3 of six patients treated with methotrexate alone) had total hair growth. Of the six who later stopped the methotrexate, three experienced a relapse. No limiting adverse effects were observed.¹⁶³ Despite the uncontrolled nature of this study, the dramatic results indicate that future studies would be warranted in a controlled setting, and that this may potentially be an effective treatment for patients with severe disease.

Also, psoralen plus UVA (PUVA) treatment, a treatment suggested to modify the immune response of the skin, has been studied for its effectiveness in alopecia areata when used in combination with corticosteroids. In

six patients with alopecia totalis and three with universalis, all achieved terminal hair growth after 2 months of treatment with minimal side effects; two patients experienced a relapse three months after termination of treatment.¹⁶⁴

A combination of 5% minoxidil with 0.5% anthralin was evaluated in 51 patients with severe treatment resistant alopecia areata who were not responsive to one or both drugs. An acceptable cosmetic response was observed in 11% of the 45 patients that completed this study, and 80% of responders maintained the growth they had. It was concluded from this study that despite the small number of subjects who were successful with this treatment, the results were superior to the use of either drug alone for these resistant patients. The synergistic effects of the two drugs could be attributed to enhanced absorption of minoxidil in the presence of an irritant dermatitis.¹⁶⁵ Another combination therapy that has shown some success for chronic severe alopecia areata is the use of topical diphenylcyclopropenone and 5% minoxidil.¹⁶⁶ The evidence for these treatments may be valuable to consider when establishing a treatment plan for patients with recalcitrant or extensive alopecia areata. Despite the limited data, these may prove to be excellent treatment options once studied more thoroughly.

"NATURAL" TREATMENTS

Modalities such as yoga, multivitamins, use of herbs, acupuncture, aromatherapy, homeotherapy are considered unconventional or alternative medicine. These therapies are more popular than ever.^{167,168}

In 1981, Rhodes et al. published a case report of regrowth in a patient with alopecia areata induced by *Primula abconia*.¹⁶⁹ The patient was first sensitized with the leaf and then applied the leaf to one side of the scalp twice a week. Hair regrowth started 1 month later and was evident 2 months later. No further evaluations of the case or investigation of the mechanism of action of the plant was performed but the result is similar to what has been described with sensitization therapy.

Eighty-six patients participated in a randomized double-blind controlled trial of aromatherapy.¹⁷⁰ In a randomized, double-blind controlled trial of 7 months' duration with follow-up at 3 and 7 months, patients massaged onto their scalp essential oils (thyme, rosemary, lavender and cedar wood) in a mixture of carrier oils (jojoba and grape seed) or only the carrier oils. Nineteen of 43 patients showed some improvement in the treatment group compared with six of 41 patients in the control group.

Onion juice (*Allium cepa L.*) has been tried to treat alopecia areata. The idea of testing this "natural" treatment came from the fact the onions and garlic belong to same genus *Allium* and garlic has been used as a topical therapy for AA as part of folk medicine.¹⁷¹ The onion juice was applied topically, twice daily, and compared to tap water applications to a group of patients with patchy disease. In

the onion juice group regrowth was seen in 73.8% of the patients at 4 weeks, 86.9% at 6 weeks whereas in the control group (tap water) the hair regrowth was apparent in only 13% of the patients at 8 weeks. This was statistically significance ($P<0.0001$). It was postulated that that onion juice might induce an immunologic reaction and stimulate hair regrowth through antigenic competition as onions belong to the genus *Allium* and are rich in sulphur and phenolic compounds.

A double-blind randomized controlled study was performed to evaluate the efficacy of topical garlic gel combined with betamethasone valerate cream in the treatment of patchy alopecia areata.¹⁷² Again, the authors proposed the study based on anecdotal data. Both groups applied topical betamethasone cream 0.1% in isopropyl alcohol twice daily for 3 months. The "active" group also rubbed garlic gel 5% on the patches of AA under dressing and left this on for 1 hour, twice daily for 3 months and the control group did the same but with a placebo gel. Hair regrowth was observed in both groups, but good and moderate responses were significantly better in the garlic/active group ($P=0.001$). The response could have occurred because of the corticoid application, but an additive efficacy of garlic was demonstrated. The mechanism of action suggested by the authors was the same for the genus *Allium*/onion juice hypothesis.

MISCELLANEOUS

Other unique therapies have been investigated for the treatment of alopecia areata. In studies with relatively small numbers of patients, isoprinosine, thymopentin, azathioprine, nitrogen mustard, and capsaicin have all been studied as potential therapies for alopecia areata. All have shown some efficacy but results need to be supported by randomized, placebo-controlled trials. In contrast, treatments that have shown no benefit or proven efficacy include the use of the vitamin D analog calcipotriol, intralesional interferon alpha-2, croton oil. Sodium lauryl sulfate, benzyl benzoate, phenol, staphylococcus-streptococcus vaccine, dapson, griseofulvin, topical tretinoin, and relaxation.¹⁷³⁻¹⁸⁹

Other treatments of interest include cryotherapy, hypnosis, and the administration of antidepressants. Cryotherapy was attempted in 112 patients with extensive alopecia areata. Liquid nitrogen was applied lightly to the affected areas once weekly for 4 weeks. Results were encouraging, with 97.2% of patients achieving new terminal hair growth. In the 6-12 month follow-up period, relapses only occurred in three of 66 patients. Side effects were mild and included those typically associated with cryotherapy, including mild swelling, itching, and sensitivity. Hair growth was also attained in the placebo group but only in 35% of patients, a statistically significant difference. This treatment may be a promising, simple, and convenient option once more studies can confirm its efficacy and safety, as well as comparing results in patients with different disease severity.¹⁹⁰

As some patients report flares of alopecia areata coinciding with episodes of stress, some studies have focused on the psychological aspects of alopecia areata. Hypnotherapy was attempted in one study on five patients with chronic recalcitrant disease; after 10-12 weekly sessions of hypnotherapy, only one had a significant increase in hair growth.¹⁹¹

What We Know

- There is a high proportion of spontaneous recovery among alopecia areata patients, with 34% to 50% of the patients recovering within 1 year without treatment and up to 90% of patients with limited scalp involvement are said to experience spontaneous regrowth within 2 years. Differences in the response to treatments are observed between patients with limited scalp involvement and patients with alopecia totalis and universalis. Patients with limited scalp involvement patients generally respond favorably to a variety of treatments.²⁻⁴
- A review of treatments for alopecia areata is a valuable and helpful tool in the decision making process for the selection of an approach to manage patchy or extensive disease in children or adults. Several studies since 1994 have incorporated the recommendations for clinical trials from the National Alopecia Areata Foundation providing standardization and a better ability to compare study design and results. The finding of important genes in alopecia areata has led to investigators discussing studying drugs that target specific pathways.
- New drug treatment opportunities based on the results of a genome-wide association study, which implicate T-cell and NK-cell activation pathways are leading to new approaches in future clinical trials of alopecia areata. Special attention is being given to the UL 16-binding protein (ULBP3) gene cluster on chromosome 6q25, as these genes make the NKGD-activating ligand or signal, which can trigger the NKG2D receptor, initiating an autoimmune response.¹ ULBP3 expression has also been found in hair follicles in scalp biopsy specimens from patients with active disease.
- Future treatment approaches for alopecia areata will most likely include the study of drugs that block the NKGD-activating ligand and NKG2D receptor interaction, halting activated T cells or modifying the inflammatory cytokine network. Many drugs currently being used or being evaluated for other autoimmune diseases, which work through these mechanisms might prove to be very effective in alopecia areata. New clinical trials will take into consideration past experiences and the utilization of the Severity in Alopecia Scoring Tool, to standardize the description of disease extent and response to therapy.

This, however, was a very small sample size and is likely not adequate to draw conclusions from. A subsequent study of 28 patients with refractory, extensive alopecia areata showed scalp hair growth of 75%-100% in 12 patients after 3 to 8 sessions of hypnotherapy, total growth occurred in nine of these. However, other treatments were not discontinued for the duration of hypnotherapy and their effect cannot be excluded.¹⁹² A larger, randomized, controlled study to confirm these results and to evaluate the long-term efficacy would be useful to confirm hypnotherapy as an effective adjunct treatment.

Antidepressants have also been studied in the hope that ameliorating some of the anxiety associated with this disease would result in hair regrowth. An evaluation of imipramine in a double blind, placebo-controlled study showed clinically significant hair regrowth in five of the seven patients, who were treated, with none in the placebo group showing regrowth.¹⁹³

SSRIs in particular have also been of interest to investigators. In one case, series investigators used citalopram in four female patients diagnosed with anxiety or depression. Overall mood improvement and objective hair regrowth was evident after 30-45 days of treatment.¹⁹⁴ A double-blind, placebo controlled study of paroxetine in 13 patients with alopecia areata and an additional psychiatric diagnosis has been completed. Two of the eight patients receiving paroxetine achieved complete regrowth of hair; four had partial regrowth; one patient from the placebo group had regrowth of hair.¹⁹⁵ In another reported case, paroxetine in a woman was administered to a patient with moderate alopecia areata and a diagnosis of major depression. In conjunction with intralesional triamcinolone, hair regrowth began in the fifth week of treatment and psychiatric health improved.¹⁹⁶ For patients with a simultaneous psychiatric condition, the use of an antidepressant may serve to improve hair growth as well as mental health, however larger studies are necessary because the sample sizes of currently available studies are not sufficient.

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Treatment of Female Androgenetic Alopecia

20

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INTRODUCTION

Female pattern hair loss (FPHL) as a distinctive entity was first described about 30 years ago. The term “androgenetic alopecia” is a debatable term because hair loss does not necessarily only occur in women with hyperandrogenemia. Although balding has been observed in hyperandrogenic women who often have other manifestations of androgen excess like hirsutism or menstrual disorders, or severe and recalcitrant acne, However some studies have detected normal androgen levels in many women with pattern hair loss.^{1,2} Genetic susceptibility also has not been recognized as a leading factor in many patients.³ Thus, the term FPHL is preferred.⁴

EPIDEMIOLOGY

Female pattern hair loss may begin at any time after menarche or adrenarche and its frequency and severity usually increases with age, from 3-6% in women aged less than 30 years to 29-42% in women greater than 70 years.^{5,6} In some such cases, the clinical impact of hair loss has considerable societal and psychological costs for patients.⁷

CLINICAL MANIFESTATIONS

Female pattern hair loss usually presents with progressive thinning and loss of hair over the crown and frontal scalp. The frontal hairline is usually preserved in patients with FPHL. The affected zone varies from merely a small area to the entire scalp. In contrast to its frequent involvement in male pattern hair loss, vertex is rarely affected in FPHL.⁸ Several classification methods of pattern hair loss have been suggested, which all have limitations.^{4,9,10} FPHL can be observed in men as an uncommon presentation of hair loss.⁸

DIAGNOSIS

The diagnosis of FPHL is based on the clinical pattern of hair loss. Laboratory evaluation of women presenting with hair loss should be pursued after ruling out any other possible differential diagnoses like telogen effluvium,

diffuse, or reverse ophiasis alopecia areata, etc. Screening tests usually include CBC, work-up for iron deficiency, and hypothyroidism. In a subset of women who show other features associated with androgen excess such as hirsutism, menstrual irregularities, or difficult-to-treat acne, testosterone, dehydroepiandrosterone sulfate (DHEAS) and sex hormone binding globulin (SHBG) should also be measured as a screening tool for making the diagnosis of possible underlying disorders.⁸

TREATMENT

Many different forms of treatment and a variety of protocols have been tried for FPHL. The most commonly used include antiandrogens (topical or systemic) and topical minoxidil.⁸

Question: How do antiandrogens and minoxidil compare in efficacy and safety to placebo in the treatment of FPHL?

METHODS

Inclusion Criteria

Since no published systematic review on this topic existed, the main sources of evidence were individual RCTs. Only RCTs concerning treatment of FPHL in women were included. The studies reporting less than 10 patients were excluded. The search became limited to full-text articles in English.

Search Methodology

To locate all studies apropos of FPHL in women, a preliminary search was carried out in the following databases (to November 2008): Ovid MEDLINE, PubMed MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL).

Search strategy to locate RCTs in Ovid and PubMed MEDLINEs was based on the Cochrane Highly Sensitive Search Strategy for identifying randomized trials in MEDLINE: sensitivity- and precision-maximizing version (2008 revision), using following key (filter) words in their special format for each MEDLINE:

- Randomized controlled trial OR Controlled clinical trial OR randomized OR placebo OR clinical trials as topic OR randomly OR trial AND humans.
- Search strategy to locate FPHL in women in all databases was androgen* OR male pattern OR female pattern OR hereditary AND alopecia OR hair loss OR baldness AND female OR woman OR girl).

After initial search, the titles and abstracts of extracted articles were re-examined. If it was determined that a clinical trial had not been relevant to nonsurgical interventions in FPHL treatment in women, it was excluded before appraisal. Two researchers assessed the included studies independently of each other to determine the articles which were completely related to the subject and were accurately performed methodologically. In addition, references of relevant articles and reviews were checked manually in search of additional sources.

Data Collection

The features considered in the assessment of quality and correctness of studies according to Jadad criteria¹¹ were:

1. Application of randomization methods to divide participants into groups.
2. Allocation concealment method of study, which is considered sufficient if the intervention in each participant cannot be predicted.
3. Blinding: Has blinding been employed in study or not and who has become blinded (i.e., participant, physician, results assessors, analyzer, or health care provider)?
4. How many participants have been excluded and have the participants been analyzed based on primary group to which they were assigned in randomization or not?
5. Intention to treat analysis; proper and enough follow up.

In the process of selecting the relevant studies, disagreements among authors were resolved by reaching consensus.

Next step was extraction of necessary data, which was also performed independently by two authors, and exchange of ideas between all authors solved disagreements. According to the assessments, a description of quality for each selected article was issued and a Critical Appraisal Topic (CAT) form was provided for each article.

Data Analysis

The gathered data were entered into Review Manager (RevMan) software, version 5.0.25 (Copenhagen: The

Nordic Cochrane Centre, 2010) for statistical analysis. Inverse variance method was used to pool the data. Statistical heterogeneity was assessed using I^2 statistic. If substantial heterogeneity (I^2 statistic > 50%) existed between studies, we would explore the reasons for heterogeneity; such as disease severity, dosage, and duration of treatment as well as disease subtypes. The data were pooled and analyzed when I^2 statistic was less than 80%. The effects of therapeutic methods in different studies were compared using a random effects model. For dichotomous results, relative risk (RR), and 95% confidence interval (CI) were reported. For continuous results, weighted mean of difference (WMD, CI 95%) were reported.

RESULTS

Included Studies

Figure 20-1 shows the number of articles obtained from the preliminary search, number of articles included for systematic review, and the number of excluded articles and the reason for exclusion. No additional articles were identified by hand searching. Table 20-1 shows the characteristics of 12 articles included in this systematic review as well as the summarization of their main findings.¹²⁻²³ Assessment of methodologic quality of these studies based on the Jadad assessment scale is presented in Table 20-2. In 11 of these 12 studies, patient selection was based on physical examination and distinctive features of female pattern hair loss and only one study exclusively included hyperandrogenic women. Various methods were used for assessing the effect size of interventions in these studies that makes any comparison impossible.

Premenopausal Women

In seven studies, patient selection was only based on the distinctive features of female pattern hair loss and patients were not screened for hyperandrogenism. In 6 studies with a total of 1378 patients, topical minoxidil (1 ml) 1%,¹⁷ 2%,¹²⁻¹⁶ and 5%¹⁶ were compared to placebo. Minoxidil vs. placebo were applied twice daily for 24 weeks¹⁷, 32 weeks¹²⁻¹⁵, or 48 weeks¹⁶. Minoxidil was superior to placebo in all but one trial.¹³ Figure 20-2 demonstrates efficacy of Minoxidil 2% in comparison with placebo after pooling the data of 5 trials.¹²⁻¹⁶ In the only minoxidil dose-finding trial, minoxidil 5% was more effective than minoxidil 2%; however, the difference was not statistically significant.¹⁶

In a double-blind, randomized, placebo-controlled study on 40 women with diffuse or androgenetic alopecia, 1 mL of a 0.1% melatonin or placebo solution was applied on the scalp once daily in the evening for 6 months.²⁰ The trichograms showed a significant increase in anagen hair rate in occipital hair of those with androgenetic alopecia treated with melatonin compared with the placebo group. The increase in anagen hair rate in frontal hair in women

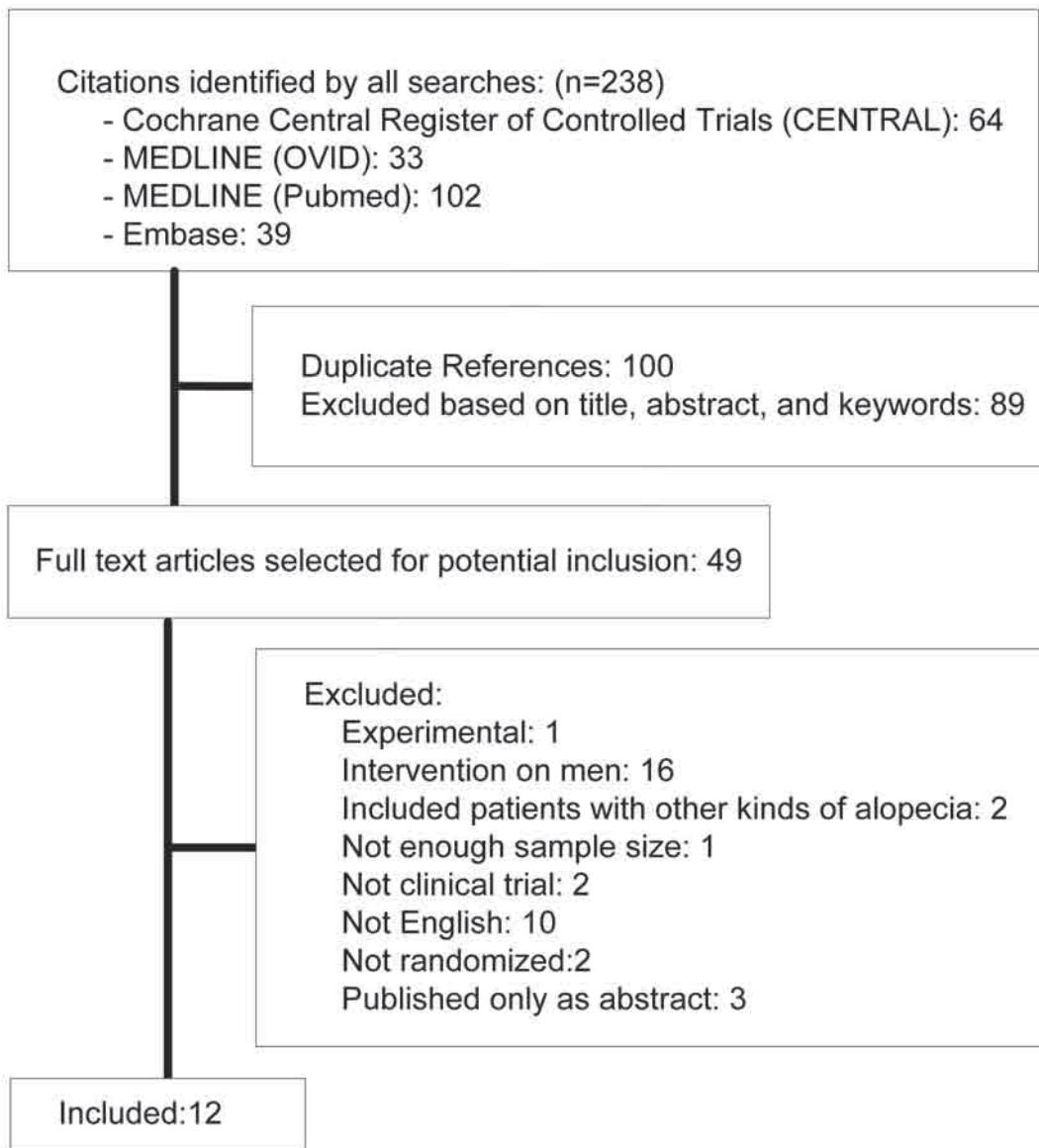


FIGURE 20-1 Flow Diagram

with androgenetic hair loss was not significantly different from the placebo group.

Vexiau P, et al.¹⁸ studied 66 patients, 18-34 years of age, randomly assigned into two groups, with 33 receiving morning and evening local applications (2 mL)

of topical minoxidil 2%. In addition, combined oral contraceptive for 21 of every 28 days and 33 patients were treated with cyproterone acetate 50 mg/day for 20 of every 28 days plus Diane for 21 of every 28 days for 1 year. Based on phototrichogram data, the minoxidil group was

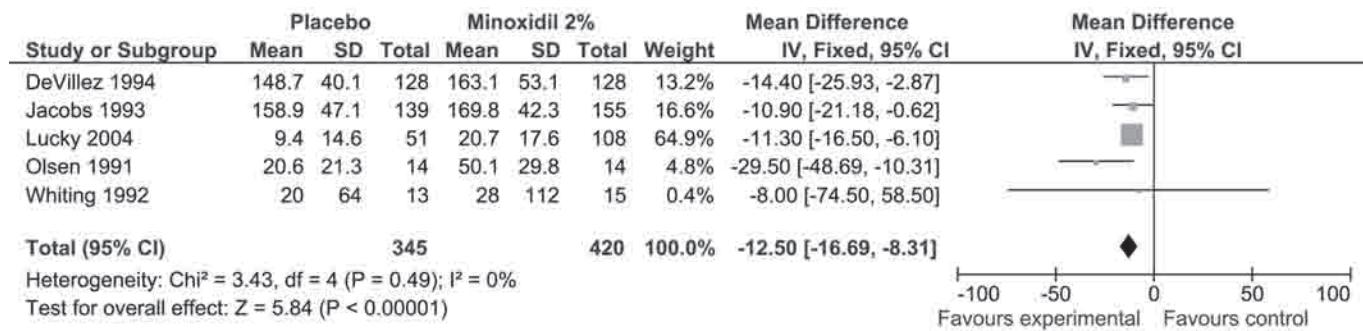


FIGURE 20-2 Forest plot of comparison: Minoxidil 2% vs. placebo, outcome: Hair count. The data of DeVillez 1994 and Jacobs 1993 studies were calculated using Hair count at 32 weeks. For the rest, Change from baseline hair count data were used.

TABLE 20-1—Characteristics of 12 Randomized-Controlled Trial for Treatment of Female Pattern Hair Loss

Ref no	Sample size*	Age (mean, years)	Ludwig	Experimental intervention	Sample size	Control	Sample size	Treatment Duration	Follow up	Primary outcome	Mean difference in change from baseline % (95% CI)
12	28	18-44	1,2	Topical Minoxidil 2% 1 mL bid	14	Placebo	14	32 weeks	-	Nonvellus hair count in 1 cm ²	29.5 (10.3 to 48.7) p = 0.006
13	28	20-44	1,2	Topical Minoxidil 2% 1 mL bid	15	Placebo	13	32 weeks	-	Nonvellus hair count in 1 cm ²	8.0 (-58.5 to 74.5) p > 0.05
14	294	18-45 (33.6)	1,2	Topical Minoxidil 2% 1 mL bid	155	Placebo	139	32 weeks	-	Nonvellus hair count in 1 cm ²	14.0 (9.6 to 18.5) p = 0.0001
15	256	17-46 (34)	1,2	Topical Minoxidil 2% 1 mL bid	128	Placebo	128	32 weeks	-	Nonvellus hair count in 1 cm ²	12.0 (5.9 to 17.5) p = 0.0004
16	261	18-49 (37)	1,2,3	Topical Minoxidil 5% 1 mL bid Topical Minoxidil 2% 1 mL bid	102	Placebo	51	48 weeks	-	Nonvellus hair count in 1 cm ²	15.1 (9.3 to 20.9) p < 0.001 [#] 11.3 (6.1 to 16.5) P < 0.001 [#]
17	273	≥20	1,2	Topical Minoxidil 1% 1 mL bid	137	Placebo	136	24 weeks	-	Nonvellus (hairs >40 μ diameter) hair count in 1 cm ²	6.1 (3.3 to 9.0) p < 0.001
18	52	18-34 26.4±4.8	1,2,3	Topical Minoxidil 2% 2 mL bid + Oral combined OCP Daily for 21 of 28 days	27	Oral cyproterone acetate 50 mg daily for 20 of 28 days + Oral Combination of ethinyl estradiol & cyproterone acetate 35 μg & 2 mg daily for 21 of 28 days	25	12 months	-	Hair (>40 μ diameter) count in 0.36 cm ²	8.9 (5.0 to 12.8) p < 0.001
19	48	25±2	1,2,3	Cyproterone acetate 50 mg day 5-15 of cycle + Ethinyl estradiol 25 μg day 5-25 of cycle Flutamide 250 mg/day Finasteride 5 mg/day	12	No treatment	12	12 months	-	Ludwig score	8 [†] 17 [†] -1 [†]

20	12	20-70	-	Topical 0.1% melatonin-alcohol solution 1 mL daily	6	Placebo	6	6 months	-	Anagen hair count	Occipital: 2.9 [§] Frontal: -4.5
21	125	41-60	1,2	Oral Finasteride 1 mg/day	62	Placebo	63	12 months	-	Hair count in 1 cm ²	-2.1 (-18.7 to 14.6) $P > 0.05$
22	62	48-71	-	Estradiol valerate 0.03% (12w) Estradiol valerate 0.03% (24w)	23 20	Placebo	20	24 weeks	6 months	Mean anagen/telogen ratio	42.4 [†] 48.3 [†]
23	70	49-72	1,2	Topical fulvestrant 70 mg/mL 30 µL/cm ² bid	34	Placebo	36	16 weeks	-	Hair count in 1.8 cm ²	-1 [†]

* Final number of participants evaluable

[†] CI is not calculated due to lack of SD report in the paper

[#]Minoxidil 5% vs. 2%; 3.80 (-1.6 to 2.9), $P > 0.05$

[§]The odds ratio of anagen to nonanagen hairs in melatonin-treated women showed a significant effect at 1.90 (95% confidence interval: 1.22-2.96; $p=0.012$) compared with the placebo-treated women in occipital area but it was 0.91 (95% CI: 0.52-1.61; $p > 0.05$) in frontal area.

TABLE 20-2—Quality Assessment of Randomized-Controlled Trials for Treatment of Female Pattern Hair Loss According to Jadad Criteria

Ref. No	Author(s) Year	Jadad Scale					
		Randomization	Blinding	Randomization description*	Blinding Description	Withdrawal description	Total
12	Olsen EA 1991	1	1	0	1	0	3
13	Whiting DA and Jacobson C 1992	1	1	0	0	1	3
14	Jacobs JP, et al., 1993	1	1	0	0	1	3
15	DeVillez RL, et al., 1994	1	1	0	0	1	3
16	Lucky AW, et al., 2004	1	1	1	1	1	5
17	Tsuboi R, et al., 2007	1	1	0	1	1	4
18	Vexiau P, et al., 2002	1	1	1	1	1	5
19	Carmina E and Lobo RA 2003	1	0	0	0	No [†]	1
20	Fischer TW, et al., 2004	1	0	0	0	1	2
21	Price VH, et al., 2000	1	1	0	1	1	4
22	Georgala S, et al., 2004	1	0	0	0	1	2
23	Gassmueller J, et al., 2008	1	1	1	1	1	5

*Information given about generation of randomization sequence

[†]No withdrawal from the beginning of study reported.

superior to the cyproterone group. This was seen in the increase in hairs of diameter >40 µm and the total number of hairs in the minoxidil group. However, in subgroup analysis, the minoxidil group was more effective in patients with isolated alopecia and in the absence of menstrual cycle irregularities and other signs of hyperandrogenism. The cyproterone acetate was also more effective when menstrual cycle irregularities and other signs of hyperandrogenism were present and when the BMI was elevated.

Carmina and Lobo,¹⁹ randomized 48 women with alopecia and increased serum androgens (testosterone, free testosterone, DHEAS) higher than the mean \pm 2 SD to one of three treatments. Twelve were treated with cyproterone acetate 50 mg/day from day 5 to day 15 of the cycle, and ethynodiol diacetate 25 µg from day 15 to day 25 of the cycle, 12 were treated with flutamide 250 mg/day, 12 were treated with finasteride 5 mg/day, and all for 1 year. Twelve patients who were recruited for the study refused any treatment and were observed without any treatment for 1 year. Thirty normal ovulatory women, matched for age and weight, were used as controls. After 1 year, only patients treated with flutamide was modestly superior to the control group, whereas finasteride and cyproterone were not effective.

Postmenopausal women

Three studies only included 282 postmenopausal women:²¹⁻²³

In one study, oral administration of finasteride 1 mg/day for 12 months did not increase hair growth or slow the progression of hair thinning in postmenopausal women with androgenetic alopecia.²¹

In the second study, estradiol valerate 0.03% was applied as 15 drops on the affected area of the scalp, every day for 4 weeks, and then every other day for 12 or 24 weeks.²² The results suggested that estradiol valerate was significantly more effective than placebo regarding anagen/telogen ratio. Furthermore, a 12-week course of estradiol valerate did not differ significantly from a 24-week course.

Additionally, 30 µl/cm² of fulvestrant 70 mg/mL solution, twice daily for 16 weeks was not associated with any statistically significant differences in favor of its use over placebo.²³

Another study,¹⁷ also included women 20 years of age and older with the average of 56-57 years old; however, the results have not been presented according to menstrual status and therefore, postmenopausal women cannot be identified.

DISCUSSION

Female pattern hair (FPHL) loss is a common disease. The role of androgens in this disease is not clear. In one study, only 40% of women with FPHL had elevated serum androgens.¹ In another study, patients with alopecia had lower serum levels of androstenedione and dehydroepiandrosterone sulfate (DHEAS), lower salivary testosterone, and

higher levels of sex hormone-binding globulin than patients with hirsutism, but total testosterone was not significantly different.² So the term FPHL has replaced the older term of androgenetic alopecia.⁸ Few RCTs for the treatment of FPHL were found in our search in English literature.^{12–23} The response to treatment may differ in patients with hyperandrogenism, and in postmenopausal women.

Premenopausal Women Without Hyperandrogenism

Seven RCTs have included women with FPHL without any evaluation of hyperandrogenism.^{12–17,20} The diagnosis in these studies were only based on the clinical pattern of hair loss. In five of these studies, twice-daily application of 1 mL of minoxidil 1%^{12,17} or 2%^{13–15} was compared with placebo. The duration of treatment was 24 weeks in one RCT¹⁷ and 32 weeks in three RCTs.^{12–14} In all of these studies, except one¹³, minoxidil was more effective than placebo in reduction of hair loss and increase in hair growth. No follow-up after discontinuation of treatment was reported in any of them.

In one dose finding RCT¹⁶, minoxidil 5% induced more hair regrowth than minoxidil 2% after 48 weeks, but the difference was not statistically significant. In men with male pattern hair loss minoxidil 5% was proved more efficacious than 2%.²⁴

No serious systemic side effect has been reported with topical application of minoxidil. It may cause redness and itching of scalp in approximately 5% of women. This dermatitis is usually a nonspecific irritant contact dermatitis, although rare cases of true allergic contact dermatitis with minoxidil have also been reported.²⁵ Hypertrichosis of face and body may occur, which is more frequent with 5% minoxidil and in patients with dark complexion.⁸ It usually subsides after discontinuation of treatment.

The mechanism of action of minoxidil in FPHL is not completely understood. Several mechanisms have been proposed including vasodilation, angiogenesis, enhanced cell proliferation, and DNA synthesis, potassium channel opening, antiandrogen effect, collagen synthesis suppression, and immunosuppression.²⁶

Although a 1-year prospective study did not find any adverse pregnancy outcome in women using topical minoxidil,²⁷ it is considered as pregnancy category X and should not be used by pregnant or lactating women.

In one RCT including 66 women with FPHL,¹⁸ treatment with 1 mL minoxidil 2% applied twice daily plus combined oral contraceptive for 21 of every 28 days was compared to cyproterone acetate 50 mg/day for 20 of every 28 days, plus Diane for 21 of every 28 days. The duration of treatment was 12 months and no follow-up was reported. Hair counts in phototrichography showed better response to minoxidil. In subgroup analysis, response to minoxidil was better in patients who had normal menstruation

cycle, but in the group treated with cyproterone, more hair growth was observed in patients who had an abnormal menstruation cycle. Patients included in this study were not assessed for the level of serum androgens.

One RCT did not find any significant difference between topical melatonin 0.1% solution, applied once mL daily and placebo after 6 months in frontal area, which is androgen dependent. Although melatonin was more effective in the occipital area.²⁰ Interestingly, the same study showed more efficacy of melatonin compared to placebo in the frontal area, but not in the occipital area in women with diffuse hair loss. In vitro studies have shown a positive effect of melatonin on hair matrix cell proliferation and hair growth, and an induction of anagen phase.²⁰

Premenopausal Women With Hyperandrogenism

Only one RCT has included exclusively patients with definite evidence of hyperandrogenism who had serum level of DHEAS, testosterone, and free testosterone more than twice of standard deviation of mean in normal controls.¹⁹ Forty eight patients were treated in three equal groups with cyproterone acetate 50 mg/day from day 5 to day 15 of the cycle, and ethinyl estradiol 25 µg from day 15 to day 25 of the cycle, or with flutamide 250 mg/day, or with finasteride 5 mg/day and 1 group was left untreated as control. The duration of treatment was 1 year. At the end of the study, only patients treated with flutamide showed significant improvement compared to the control group. Flutamide is a strong competitive inhibitor of androgen receptors and has been used successfully for the treatment of hirsutism. Considering the risk of hepatotoxicity of flutamide,²⁸ and the prolonged duration of treatment for FPHL, flutamide cannot be a suitable option in the treatment of FPHL. Finasteride is a selective inhibitor of 5α-reductase type II and has been approved for the treatment of male pattern hair loss at a dose of 1 mg daily.⁸ Although a few case reports have shown the efficacy of finasteride in FPHL patients with or without hyperandrogenism, or postmenopausal women,^{29–31} this RCT and also another RCT in postmenopausal women²¹ could not show any superiority of finasteride over placebo.

Postmenopausal Women

Three RCTs have exclusively evaluated postmenopausal women with FPHL. In these studies, oral finasteride 5 mg daily for 12 months²¹, topical estradiol valerate 0.03% for 12–24 weeks²², and topical fulvestrant 70 mg/mL for 16 weeks²³ were compared with placebo. None of them showed any significant difference between these treatments and placebo. Fulvestrant is a ‘pure’ oestrogen receptor antagonist, which causes telogen follicles to enter anagen, thereby causing hair growth.²³

What We Know

- The only treatment shown to be effective in FPHL is topical minoxidil. It seems the effect of minoxidil is not related to age or androgen level of patients and it may be effective in women with FPHL, both with and without hyperandrogenism, and in young and old, pre or postmenopausal. The maximum duration of treatment with minoxidil was 1 year in these RCTs, and none of them included a follow-up period after discontinuation of treatment. Therefore, it is not clear how long the effect of minoxidil lasts in FPHL. Similar studies in male pattern hair loss have shown that any beneficial effect of minoxidil is lost 4-6 months after discontinuation of treatment.
- In postmenopausal women with FPHL, treatment with antiandrogens such as estradiol, fulvestrant, and finasteride was not more effective than placebo. As the mechanism of action of minoxidil is not related to androgen levels, it may be the only treatment option in these patients, although no RCT evaluating minoxidil in postmenopausal women is available.
- In patients with FPHL and hyperandrogenism, treatment with antiandrogens seems logical. However, in the only available RCT, only flutamide was effective and finasteride and cyproterone did not show satisfactory results. In women with FPHL who have regular menses and no evidence of hyperandrogenism, there is no evidence to support use of anti-androgens.

One RCT evaluating topical minoxidil included women older than 20 years with a mean age of 56-57 years¹⁷, but data on postmenopausal women were not separately reported, so no conclusion could be drawn on the efficacy of minoxidil in postmenopausal women.

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Treatment of Genital Warts

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INTRODUCTION

Human papilloma virus (HPV)-induced genital wart is one of the most common sexually transmitted disease in the United States, behind chlamydia/gonorrhea, which affected 1.5 million new patients in 2007. Its prevalence has approached 24 million in the United States alone. Every year, 0.5~1 million new cases developed (CDC estimated 5.5 million people newly affected yearly). There is a 10% lifetime risk of infection in the general population.¹ Since 1976, 120 types of HPV have been designated and characterized in a defined manner, although many more HPV types have been recognized through polymerase chain reaction (PCR) amplification products. Nearly 40 HPV types are found in genital warts. Over 90% of cervical cancers are associated with genital warts and more than half induced by HPV-16 and -18.¹

TREATMENTS

There is no effective virus-specific therapeutic agent for genital warts. Destruction or abolition of visible lesion is the goal, not the elimination of virus. *Gardasil* and

Cervarix are HPV vaccines against HPV16/18/6/11 or HPV16/18, respectively. However, they are for prevention not treatment. No matter which treatment applied, recurrence is almost certain because of the skin surrounding visible lesion carrying subclinical HPV particles. In most occasions, remission, not cure, is the reasonable prospect. Genital warts may cause discomfort, irritation, pruritus, malodor, sometimes even bleeding, and some degree of emotional distress. Thus, most patients desire treatment. The treatment chosen is in part dictated by the size of the warts, their location, and patient's gender.

THERAPEUTIC REGIMENS AND MODALITIES

There are three categories of therapeutic agents and regimens: Cytotoxic agents, physical destruction, and immunomodulation. The effectiveness in treating genital warts is represented in percentage of clearance and recurrence, which, in turn, are estimated from multiple clinical trials. (See Tables 21-1 and 21-2). The strength of medical evidence, from Level 1 to 5, and the grade of

TABLE 21-1—Treatments for Genital Warts: Regimens, Rates of Clearance and Recurrence, Grades of Recommendation and Levels of Evidence

Therapeutic Regimens/ Modalities	Method of Application	Effect [†] : Clr/Rec	Grade [‡] / Evidence
<i>Cytotoxic Agents</i>			
Podofilox 0.5% gel, cream or solution	BID for 3 consecutive days with 4 days off, weekly for 4 weeks	70%/30%	A/1 (1a-)
Podophyllin 20-25% solution	Applied to lesions, wash-off 4 hours later, once-twice weekly for 4-6 weeks	60%/40%	A/1 (1a-)
Veregen ointment (15% Sinecatechins)	TID for up to 16 wks. Only for external genital warts and perianal warts.	55%/5%	A/1 (1a)
5-FU/adrenaline gel, inj.	Intradermal gel injection, once weekly for 6 weeks	60%/50%	A/1 (1b)
5-FU(5% fluorouracil), topical	QD for 5 consecutive days or 1-3 per week for 4 weeks; wash-off after 4 hours.	45%/60%	A/1 (1a-)
Isotretinoin, oral	1 mg/kg per day for 3-5 months	50%/10%	B/3 (3a)

(Continued)

TABLE 21-1—Treatments for Genital Warts: Regimens, Rates of Clearance and Recurrence, Grades of Recommendation and Levels of Evidence (Continued)

Therapeutic Regimens/ Modalities	Method of Application	Effect†: Clr/Rec	Grade‡/ Evidence
Physical Destruction			
Excision, surgical	Excision with steel blade w/wo closure	90%/25%	B/3 (3a)
Cryosurgery (Liquid nitrogen)	Triple freeze cycles for each lesion, repeat monthly until cleared (usually, 2-3 months)	80%/30%	B/3 (3a)
Lasers	CO2 Laser, single treatment, may repeat. Pulsed dye laser	80%/30%	B/2 (2a-)
Electrosurgery	Repeat monthly until cleared, usually with curettage	80%/55%	B/3 (3a)
Trichloroacetic Acid 80-90% solution	Once weekly for 6 weeks	75%/40%	A/1 (1a-)
Immuno-modulation			
Aldara(imiquimod) 5% cream	Applied to lesions over night, 3 times per week for 4 months.	55%/20%	A/1 (1a)

†Clr/Rec: % of Clearance/% of Recurrence.

‡See Oxford EBM Levels for Treatment.

TABLE 21-2—Oxford Evidence-Based Medicine (EBM) Levels for Treatment #

Grade*	Level of Evidence	Description of Clinical Evidence
A	1	Controlled trials
	1a	Systematic reviews (with homogeneity) of randomized controlled trials
	1a-	Systematic review of randomized trials displaying worrisome heterogeneity
	1b	Individual randomized-controlled trials (with narrow confidence interval)
	1b-	Individual randomized-controlled trials (with a wide confidence interval)
	1c	All or none randomized-controlled trials
B	2	Cohort studies
	2a	Systematic reviews (with homogeneity) of cohort studies
	2a-	Systematic reviews of cohort studies displaying worrisome heterogeneity
	2b	Individual cohort study or low quality randomized controlled trials (<80% follow-up)
	2b-	Individual cohort study or low quality randomized controlled trials (<80% follow-up/wide confidence interval)
	2c	'Outcomes' Research; ecologic studies
	3	Case-control studies
	3a	Systematic review (with homogeneity) of case-control studies
	3a-	Systematic review of case-control studies with worrisome heterogeneity
C	4	Case-series (and poor quality cohort and case-control studies)
	D	Expert opinion without explicit critical appraisal, or based on physiology, bench research or 'first principles'

Adapted from the Oxford Centre for Evidence-Based Medicine. (Produced by Bob Phillips, Chris Ball, Dave Sackett, Doug Badenoch, Sharon Straus, Brian Haynes, Martin Dawes since November 1998, updated by Jeremy Howick, March 2009). (Website: <http://www.cebm.net/index.aspx?o=1025>).* Four **Grades** of Recommendation for treatments, from A to D (graded by the U.S. Preventive Services Task Force, reflected the strength of evidence and magnitude of net benefit): e.g., Grade A is consistent with Level 1 evidence.

recommendation for treatment, from Grade A to D, are based on Oxford Evidence Based Medicine (EBM) Levels for Treatment from *the Oxford Centre for Evidence-Based Medicine*.

Cytotoxic Agents

Condylox (Podofilox) 0.5%²

Podophyllotoxin is the most active ingredient of podophyllin. Purified podophyllotoxin 0.5% solution, cream or gel is self-applied by the patient twice a day for three consecutive days of a week in 4-week treatment cycles. No more than 10 cm² of wart tissue should be treated at one time. Local adverse reactions including erythema, pain, burning, inflammation, and erosion have been experienced by more than 50% of patients. It is not recommended for perianal, vaginal, or urethral warts. Clinical clearance approaches 70% with a 30% recurrence rate, which is better than podophyllin. Several randomized-controlled trials confirmed its efficacy: Podofilox has a Grade-A recommendation for treatment and an evidence of Level 1a-.

Podophyllin 25%³⁻⁵

Podophyllin is applied to the lesions once weekly by the physician in the office/clinic and is washed off 4 hours later by the patient. A course of six consecutive weekly treatments is recommended. Podophyllin is available as a crude resin extract in 25% concentration in tincture of benzoin. It works better on large exophytic genital warts on moist surfaces. It is not very effective on dry surfaces. Like Condylox, it is not recommended for perianal, vaginal, cervical or urethral warts, but very effective for penile warts particularly warts on the glans and under prepuce. Powdering the warts after application of podophyllin is recommended for avoiding irritation to the surrounding "normal" skin. Applying large quantities of podophyllin should be avoided. This may cause systemic toxicity through absorption. Such potential toxicity and limitation in the use in certain types of genital warts makes podophyllin an unpopular choice of treatment. Its clearance rate is 60% with a 40% recurrence rate. This regimen has been tested in many randomized-controlled and case-controlled trials. Podophyllin gains a Grade A recommendation for treatment and a Level 1a- evidence.

Veregen (15% Sinecatechins) Ointment⁶

Veregen is applied on the skin of external genital and perianal areas three times a day for up to 16 weeks. It is intended for external genital warts and perianal warts, not for lesions inside vagina, cervix, urethra, rectum, or anus. Sinecatechins is a partially purified fraction of the water extract of green tea leaves from *Camellia sinensis* (L.) O Kuntze. Veregen ointment is thus a mixture of catechins

and other green tea components. The ointment has a 55% clearance rate and a low 5% recurrence rate. Veregen has a grade-A treatment recommendation and its evidence level is 1a, the highest rating among all clinical trials assessing the efficacy of treatment.

Efudex (5% fluorouracil) and 5-FU injection^{7,8}

Efudex cream (or solution) is recommended as a daily application for 5 consecutive days for 4 weeks or a mere two applications per week (an intermittent therapy) for 4 weeks. This results in an unimpressive 45% clearance rate and a relatively high recurrence rate of 60%. However, it is quite effective in flat penile warts, urethral and vaginal warts. It is prone to cause severe irritation/inflammation and painful erosions, so it is advised to wash it off after 4 hours. The recommendation for treatment is Grade A with Level 1a- evidence. Carac cream (0.5% fluorouracil) has been used for genital warts, assumed it is as effective as 5-FU, but with less irritation. However, it is hardly ever used.

Intradermal injection of a 5-FU/adrenaline gel, once weekly for 6 weeks, has shown a 60% clearance rate and a 50% recurrence rate. The recommendation for treatment is Grade A. Because of a dearth of randomized clinical trials, the evidence is Level 1b. It is not a commonly used regimen.

Isotretinoin, oral⁹

The use of oral isotretinoin has only been reported in a limited number of studies with mediocre effect (50% responsive rate and 10% recurrence rate). It is seldom used. Topical retinoids are not effective in genital warts.

Physical Destruction

Excision, surgical¹⁰

Surgical excision can efficiently eliminate genital warts (90% in effectiveness) particularly for large, exophytic or extensive lesions but cannot prevent it from recurring (25% recurrence rate). This method is often combined with electrosurgery. There were no randomized-controlled trials on surgical intervention, so the evidence level is slightly lower at 3a.

Cryosurgery (Liquid nitrogen)^{3,4,11}

Cryotherapy (mainly, liquid nitrogen) is more effective than podophyllin/podophyllotoxin, approaching 80% resolution and 30% recurrence. Three freeze-thaw cycles are applied to each lesion every month for 3 months resulted in a necrosis of wart tissue and formation of crusts, which usually fell off in 2-3 weeks. A zone of 1 mm beyond the

lesion is frozen. Cryotherapy is safe to use in pregnant patients. It is best for small, flat, or popular genital warts, not large exophytic lesions.

Laser vaporization¹²

The use of CO₂ laser in the treatment of genital warts has not been demonstrated to be more effective than simpler surgical or electrosurgical methods. The clearance rate is 80% with a recurrence rate of 30%. The CO₂ laser has the advantage of working on a bloodless field, healing rapidly with minimal scarring and focusing on lesions with precision. However, it might generate a smoke plume containing viral particles potentially infectious to the surgeon. Thus, surgeon should exercise precaution by wearing face mask and using smoke evacuator to remove the plume. Decontamination of the equipment after the surgery should be done. Laser treatment is recommended in vaginal, vulvar, and anal warts. It has been used for large and extensive genital warts with success.

A newer approach, photodynamic therapy with topical 20% 5-aminolaevulinic acid (ALA) solution applied to lesions under occlusive dressing and irradiation with helium-neon laser (100 J/cm² and a power of 100 mW), leads to clearance of condyloma acuminata in 100% (6% recurrence rate).¹² This therapy needs more clinical trials to confirm its efficacy. A recent randomized double-blinded prospective study on 175 patients treated with ALA-PDT plus CO₂ laser versus CO₂ laser alone showed no difference between them in controlling recurrence.¹³ The recurrence rate 12 weeks after either treatment was about 50%.¹³

Electrosurgery³

Electrocauterization/electrofulguration is quite effective: clearance therapy is 80% and cure at 55%. It is often used for recurrent warts or when other methods failed to result in "cure." HPV DNA is detected in the plumes generated during electrocauterization treatment just like during CO₂ laser treatment. This old-fashioned but time-honored treatment lacks randomized-controlled trials, thus its evidence level is lower at 3a just like surgery.

Trichloroacetic acid (TCA)¹¹

Trichloroacetic acid in 80~90% solution can be applied to genital warts weekly for 6 weeks. TCA causes tissue destruction. It is most effective on small, moist warts. It is effective in 75% of patients with a recurrence rate of 40%. The efficacy of treatment gained some support from a couple of randomized-controlled trials but its use has been limited because of its causing ulcerations and pain. It is safe for use in pregnant patients. TCA has a Grade-A recommendation for treatment and an evidence of Level-1a-.

Immunomodulation

Aldara(Imiquimod 5%)^{14,15}

Imiquimod, an immune response modifier that induces IFN locally at the site of application, has an efficacy of 55% and yields a low recurrence rate of 20%. Many high-quality randomized clinical trials earned it the highest evidence level (1a) and a grade-A treatment recommendation.

Aldara is a 5% imiquimod cream available in a box of 12 or 24 single-use packets. One packet can cover up to 30 cm² when applied appropriately. It is patient self-applied, three days (at bedtime) a week for 16 weeks. The treated areas should be cleansed the next morning. Response is slow, requiring 10 or more weeks in some patients to see results. The application might result in significant irritation, inflammation, and erosion. Imiquimod is often used for penile, perianal, and vulvar condyloma. It is not recommended for pregnant women.

IFN- α therapy^{16,17}

The efficacy of systemic and intralesional IFN- α therapy has been found to be ineffective in eradicating genital warts (a mere 35% clearance rate). Several randomized clinical trials have failed to confirm the efficacy of intralesional IFN- α . Some experts would no longer recommend a routine clinical use of this expensive regimen. However, IFN- α 2b cream has revived the hope of yet another immunomodulation therapy for genital warts. In clinical trials, IFN- α 2b cream is applied 3 times a week for 6 weeks and shows a 60% clearance rate and 10% recurrence. The treatment recommendation is Grade A and evidence level is 1a-. FDA is considering its approval.

Cidofovir 1% gel¹⁸

Cidofovir topical gel applied 5 days a week for 6 weeks has a 52% clearance rate and 20% recurrence rate. It has a Grade A treatment recommendation and Level 1b- evidence. It is expected to be approved by FDA by the end of 2009.

SPECIAL CONSIDERATION

Genital Warts in Children

Genital warts in children could arise from social nonsexual contact or serious, sexual abuse. Children can acquire genital warts through vertical transmission (from infected pregnant mother), particularly in children younger than 1 year of age. Infants might get genital warts from digital inoculation (from adults' infected fingers). In older children, autoinoculation through their own infected fingers might happen. Genital warts in children from nongenital source, like hand warts, tend to be small, digital, nonexophytic and limited in size and areas involved. However, through HPV

typing, many children's genital warts have the same types of genital HPV found in family members who had genital HPV infection. Even so, there needs to be solid evidence to determine sexual abuse. For instance, the HPV type in children's genital warts matched with the alleged abuser's HPV type. In abuse cases, other STDs should be screened for.

Genital warts in children often resolve without treatment in a majority of cases. Aggressive approach is discouraged. Nonintervention might be a reasonable approach. Topical therapy, such as podofilox, TCA, veregen, or imiquimod should be tried first.

Genital Warts in Pregnant Women

Genital warts have a tendency to enlarge and proliferate during pregnancy. Its removal is thus advocated. The use of podophyllin and podofilox is contraindicated during pregnancy. Laser, surgery, cryosurgery, and TCA are safe and effective in treating pregnant patients. Cesarean section should not be recommended solely for the reason of preventing infant's laryngeal papilloma.¹⁹

Genital Warts in Sexual Partners

Examination of sexual partners for clinical or subclinical HPV infection is highly recommended. The treatment, whichever chosen, should be discussed with patient's sexual partner, not just patient himself/herself. Transmission between partners ought to be prevented by exercising proper protection measures. Treatment for both patient and partner(s) is stressed.

HPV Vaccination

The HPV major capsid protein, L1, can spontaneously self-assemble into virus-like particles (VLPs) that resemble genuine HPV virions. Since these VLPs do not carry real copy of HPV DNA, they cannot induce squamous intraepithelial neoplasm or cancer. However, they can elicit an

What We Know

- Among all self-applied regimens, Condylox (podofilox) gel/cream/solution is the best and very easy to apply. Aldara cream is not better. Also, Aldara remains a problem to some patients as not every insurance plan covers it. This makes it a very expensive alternative. The new Veregen ointment has a very low recurrence rate but needs long-term follow-up data to prove its efficacy.
- Physical destruction is far better than self-applied regimens. However, the recurrence rate stays high. This makes the search for a better eradication modality a priority.

antibody response in vaccine recipients against infection by the HPV types exemplified in the vaccine. *Gardasil* is the first HPV vaccine against HPV16/18/6/11. It contains recombinant VLPs assembled from the L1 proteins of HPVs 16, 18, 6 and 11. Three shots (on day one, month two, and month 6) can accomplish nearly 100% prevention. This and another just approved HPV vaccine, *Cervarix*, against HPV 16/18, are recommended for females aged 9-25 and males aged 9-26.

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Treatment of Nongenital Warts

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INTRODUCTION

Warts are benign proliferations of skin and mucosa caused by the human papilloma virus (HPV). More than 100 types of HPV have been identified. Although certain HPV types tend to occur at particular anatomic sites, warts associated with any HPV type may occur at any site. Frequent clinical manifestations of HPV infection include common warts, genital warts (see Chapter 21), flat warts, and deep painful palmoplantar warts (myrmecia). Less common manifestations of HPV infection include focal epithelial hyperplasia (Heck disease),¹ epidermodysplasia verruciformis, and plantar cysts. Warts are transmitted by direct or indirect contact. Predisposing factors that invite infection include disruption to the normal epithelial barrier. Common warts are usually asymptomatic, but they may cause cosmetic disfigurement or tenderness. Plantar warts on weight-bearing surfaces of the sole can be painful, and extensive involvement may impair ambulation. Malignant transformation in nongenital warts is rare but does occur and is known as verrucous carcinoma.²⁻⁴ Verrucous carcinoma is a slow-growing, locally invasive, well-differentiated squamous cell carcinoma that may be easily mistaken for a common wart. It can occur anywhere on the skin but is most common on the plantar surface of the sole. Although this type of cancer rarely metastasizes, it can be locally destructive and should be excised. Because of this entity, consider a deep incisional biopsy of any lesion that is extensive and not responsive to treatment. Treatment of warts can be difficult, with frequent failures and recurrences. Many warts, however, resolve spontaneously within a few years, as delayed cellular immunity to the wart virus takes effect.

EPIDEMIOLOGY

Warts are widespread worldwide and are estimated to affect approximately 7-12% of the population.⁵ They are more common in school-aged children with a prevalence of 10-20%.⁶ Increased frequency of warts also occurs among immunosuppressed patients and meat handlers. HPV is spread by direct skin-to-skin contact or indirect contact through fomites. It is hardy and can resist desiccation, freezing, and prolonged storage outside of host cells.

Autoinoculation also may occur when immune response is low, causing local spread of lesions. The incubation period for HPV frequently ranges from 1 to 6 months, but latency periods of up to 3 years or more are suspected to occur. With respect to race, common warts appear approximately twice as frequently in whites as in blacks or Asians.⁷ Focal epithelial hyperplasia (Heck disease) is more prevalent among American Indians and Inuit.¹ With respect to sex, the male-to-female ratio approaches 1:1. Nongenital warts can occur at any age. They are unusual in infancy and early childhood, increasing among school-aged children, and have a peak incidence at 12-16 years.⁸ The incidence of nongenital warts then generally declines slowly with age.

ETIOLOGY

Warts are caused by HPV, a double-stranded, circular, supercoiled DNA virus enclosed in an icosahedral capsid with 72 capsomers. Warts can infect any area on the skin or mucous membranes. The infection is confined to the epithelium and does not result in systemic dissemination of the virus. Replication occurs in differentiated epithelial cells in the upper level of the epidermis, although viral particles can be found in the basal layer. More than 100 types of HPV have been identified. They are numbered in the order of their discovery based on genotype, with at least 10% difference required in the nucleotide sequences compared to other types.⁹ They include those that cause common warts, most commonly HPV types 2 and 4, followed by types 1, 3, 27, 29, and 57. Deep palmoplantar warts (myrmecia) are most commonly associated with HPV type 1, followed by types 2, 3, 4, 27, 29, and 57. Flat warts are caused by HPV types 3, 10, and 28. Butcher's warts are associated with HPV type 7. Focal epithelial hyperplasia (Heck disease) is caused by HPV types 13 and 32. Cystic warts are associated with HPV type 60. A few HPV types are associated with the development of malignancies, including types 6, 11, 16, 18, 31, and 35. This malignant transformation is seen most commonly in patients with genital warts (see Chapter 3.24) and in immunocompromised patients. In patients with epidermodysplasia verruciformis, HPV types 5, 8, 20, and 47 have oncogenic potential.

DIAGNOSIS

Common warts, known as *verruca vulgaris*, appear as hyperkeratotic papules with a rough, irregular surface. They range from smaller than 1 mm to larger than 1 cm. While they can occur on any part of the body, they are seen most commonly on the hands and knees at sites of prior minor trauma. The diagnosis of warts is made primarily based on clinical findings.^{10,11} Paring of warts may reveal minute black dots, which represent thrombosed capillaries. Obtain a biopsy if the diagnosis is in doubt. In addition, immunohistochemical detection of HPV structural proteins may confirm the presence of virus in a lesion, but this has a low sensitivity. Viral DNA identification using Southern blot hybridization is a more sensitive and specific technique used to identify the specific HPV type present in tissue. Polymerase chain reaction may be used to amplify viral DNA for testing. Although HPV may usually be detected in younger lesions, it may not be detectable in older lesions. Filiform warts are long slender thread-like growths, usually seen on the face around the lips, eyelids, or nares. Deep palmoplantar warts (*myrmecia*)¹² begin as small shiny papules and enlarge to become deep endophytic, sharply defined, round lesions with a rough keratotic surface, surrounded by a smooth collar of callus. They tend to be more painful than common warts, especially those that occur on the plantar surface on weight-bearing areas, such as the metatarsal head and heel. When palmoplantar warts occur on the hand, they tend to be subungual or periungual. Flat warts or *verruca plana* are flat or slightly elevated flesh-colored papules that may be smooth or slightly hyperkeratotic. They range from 1 to 5 mm or more, and numbers range from a few to hundreds of lesions that may become grouped or confluent. While flat warts may occur anywhere, the face, hands, and shins tend to be the most common areas. They may appear in a linear distribution because of scratching or trauma (Koebner phenomenon). In men, they may be spread in the beard area by shaving. Regression of these lesions may be heralded by inflammation. Butcher's warts are seen most commonly on the hands of raw meat handlers. Their morphology is similar to common warts, with a higher prevalence of hyperproliferative cauliflower-like lesions. A mosaic wart is a plaque of closely grouped warts. When the skin surface is pared, the angular outlines of tightly compressed individual warts can be seen. Mosaic warts usually occur on the palms and soles. Focal epithelial hyperplasia (Heck disease)¹, is an HPV infection occurring in the oral cavity, often on the lower labial mucosa. It also can be seen on the buccal or gingival mucosa and rarely on the tongue. The lesions appear as multiple flat-topped or dome-shaped pink-white papules, usually 1-5 mm, with some lesions coalescing into plaques. They are seen most frequently in children of American Indian or Inuit descent. A cystic wart (plantar epidermoid cyst) appears as a nodule on the weight-bearing surface of the sole. The

nodule usually is smooth with visible rete ridges but may become hyperkeratotic. If the nodule is incised, keratinous material may be expressed. The etiology of these lesions is uncertain. One theory is that a cyst forms, originating from the eccrine duct, and secondary HPV infection occurs while another theory is that epidermis infected with HPV becomes implanted into the dermis, forming an epidermal inclusion cyst.^{13,14} Differential diagnoses for warts include acquired digital fibrokeratoma, actinic keratosis, arsenical keratosis, cutaneous horn, lichen niditus, hypertrophic lichen planus, molluscum contagiosum, prurigo nodularis, seborrheic keratosis, and squamous cell carcinoma.

SEARCH METHODS

A search was conducted using Ovid EBM Reviews - Cochrane Database of Systematic Reviews finding topical treatments for cutaneous warts¹⁵ and Ovid MEDLINE 1950 to December 2009, with extension by tracing article references back to the 1920s for treatment of warts. Of particular interest were randomized-controlled trials (RCT) and nonrandomized-controlled trials (NRCT), with case series (CS) and case reports (CR) also included for completeness.

EVIDENCE FOR TREATMENT EFFECTIVENESS

The studies reporting effectiveness of various nongenital wart treatments were rated in terms of the strength of the scientific evidence according to the American College of Cardiology and American Heart Association (ACC/AHA) guidelines grading schema.¹⁶ This involves 3 classes of recommendation 1, 2, and 3, and 3 strengths of evidence A, B, C. Recommendation class 1 is for treatments for which there is evidence or general agreement that the treatment is effective. Class 2 is for treatments where there is a divergence of evidence or opinion about the effectiveness of treatment. Class 3 is for treatments where there is evidence or general agreement that the treatment is not effective. Evidence strength level A is based on the results of multiple RCTs or meta-analyses of such trials. Level B is based on evidence from a single RCT or from NRCT studies. Level C is based on expert opinion, CS, several CR, or standards of care.

TREATMENTS

Many treatment modalities for warts are available, but none is uniformly effective.¹⁷⁻²³ It is recommended to begin with the least painful, least expensive, and least time-consuming methods, reserving the more expensive and invasive procedures for refractory extensive warts. As a rule of thumb, a single nonspread ing wart probably reflects a better cell-mediated immune (CMI) response to the wart virus, while multiple spreading warts reflects less CMI response.²⁴

Treatment options include benign neglect. Providing no treatment at all is certainly safe and cost effective, since 65% of warts may regress spontaneously within 2 years. Without treatment, however, warts may enlarge or spread to other areas. Treatment is recommended for patients with extensive, spreading, or symptomatic warts, or warts that have been present for more than 2 years. When warts resolve on their own, no scarring is seen. Scarring can occur as a result of different treatment methods that cause dermal injury such as strong acids, electrocautery, excision, laser, and less commonly cryosurgery. Hyperthermia involves immersing the involved surface in hot water (113° F or 45°C) for 30-45 minutes, 2-3 times per week, and has been reported to be effective in some cases in inducing wart resolution. Treatment failures and wart recurrences are common, especially among immunocompromised patients, who often are refractory to wart treatments. Normal appearing perilesional skin may harbor HPV, which helps explain recurrences. A quadrivalent vaccine (Gardasil) for HPV 6, 11, 16, and 18 has been developed and approved for prevention of genital warts (see Chapter 21), but so far no vaccine has been developed and approved for prevention of nongenital warts. See Table 22-1 for an overview of recommended first, second, and third line treatments for nongenital warts. For the most recent information on prescription medicines and their indications, interactions and adverse effects see the current Physicians Desk Reference²⁵ or similar source.

Psychological Treatment of Warts

Suggestion and the placebo effect have a long history of enhancing wart resolution both in folklore and in the medical literature. Our understanding of how CMI can be modified by the brain through psycho-neuro-endocrine effects on the immune system makes this approach biologically

plausible. There is case series supportive literature for suggestion²⁶ as evidence class 1C, and placebo has been supported by CS but is not supported by a small RCT,²⁷ placing it as evidence class 2B. There are no contraindications or adverse effects for appropriate suggestion. The same RCT²⁷ is one of several RCT that demonstrated the efficacy of hypnosis in inducing wart resolution, in this case being significantly superior to salicylic acid and placebo and control. Hypnosis for warts is evidence class 1B. Hypnosis has been used to treat warts refractory to other treatments.²⁸ Resolution rates have been reported from 27-55%, with prepubertal children more likely to respond than adults do. For warts resistant to hypnosis, a case series with resolution in 33 of 41 cases demonstrated the efficacy of psychosomatic hypnoanalysis,²⁹ with evidence rating of class 1C. Hypnosis and psychosomatic hypnoanalysis should be used only by those suitably trained and should be used with great caution in patients with psychosis. There are minimal adverse effects such as occasional posthypnotic mild headache.

Topical Agents for Nonprescription Home Use

Keratolytic agents cause cornified epithelium to swell, soften, macerate, and then desquamate. Salicylic acid (Compound W and similar) is available OTC in 5-40% concentration in creams, paints, gels, karaya gum, impregnated plasters, collodion, or sodium carboxy cellulose tape. Lactic acid may be a second keratolytic ingredient in some wart varnishes. By dissolving the intercellular cement substance, salicylic acid desquamates the horny layer of skin. Therapeutic effect may be enhanced by removal of some of the surface keratin prior to application. Dosing for adults and children is topically daily/bid for several weeks. No drug interactions are reported. Contraindications include documented hypersensitivity, prolonged use in diabetics or those with impaired circulation. Do not use on nevi or birthmarks. Do not use on genital area, face, or mucous membranes. Do not use on irritated skin or infected skin. Precautions are pregnancy category C. Fetal risk was revealed in studies in animals but not established or not studied in humans. It may be used if benefits outweigh the risk to the fetus. Also, avoid contact with normal skin surrounding warts. Immediately flush with water for 15 min if contact with eyes or mucous membranes occurs. Avoid inhaling vapors of the solvents. Side effects may include irritation and maceration of surrounding normal skin or contact dermatitis to colophony in collodion bases. Salicylic acid is a first-line therapy used to treat warts. It is available without a prescription and can be applied by the patient at home. The local inflammatory reaction created by the treatment attracts various inflammatory cells that may in turn help to develop CMI response. Cure rates in RCT from 70-80% are reported compared with about 30-50%

TABLE 22-1—Recommended Sequencing of Treatments for Warts Along with Evidence Categories for Each

Wart Type	First Line	Second Line	Third Line
Common	Salicylic acid 1A Liquid nitrogen 1C	Imiquimod* with occlusion 1C	Contact sensitizers** 1C Hypnosis 1B
Flat	Imiquimod* 1C	Topical retinoid* unrated	Liquid nitrogen 1C
Plantar	Salicylic acid 1A Liquid nitrogen 1C	Intralesional Immuno-therapy** 2C	Bleomycin* 2A Hypnosis 1B

*Off-label

**Considered experimental

in controls. It is evidence category 1A, with multiple RCT supporting its effectiveness.¹⁵

Adhesiotherapy consists of applying duct tape to the wart daily. This method is painless and inexpensive and has published reports of good success.^{30,31} Duct tape topical occlusion of warts overnight causes the cornified epithelium to swell, soften, and macerate. Removal of the tape causes gentle tape stripping of the macerated epidermis. Mild irritation might help to induce CMI against the wart virus. However, two RCT found no significant difference between duct tape and placebo occlusion, so it is currently evidence class 3B.^{32,33} Adding various topical home remedies such as raw minced garlic or banana inner peel, lemon slice, vinegar, lime juice, raw potato slice, tea tree oil, aloe, castor oil, dandelion stem milk, crushed chickweed, or strong calendula tea applied to the wart under duct tape or adhesive tape occlusion have so far not been tested by RCT to determine if they surpass the placebo effect. Raw garlic cloves have been shown to have antiviral activity and can be rubbed onto the wart nightly, followed by occlusion.³⁴ Topical tea tree oil has also been reported as successful in some cases, evidence class 2C.³⁵

Topical Agents for Home Use by Prescription

Immunomodulators stimulate the release of key factors that regulate the immune system.¹⁹ Imiquimod (Aldara) 5% cream is an immunomodulator that is FDA approved for use for genital and perianal warts in patients 12 years or older. It induces secretion of interferon alpha and other cytokines. While it has not received FDA approval for treatment of nongenital warts, off-label use reportedly indicates successful treatment of nongenital warts in some cases.³⁶ It is dosed topically in adults and children older than 12 at bedtime, three times a week with or without duct tape or adhesive tape occlusion. More frequent use up to twice daily has been reported, but irritation may be increased with use that is more frequent. There are no reported interactions with other drugs. Contraindications are documented hypersensitivity. Precautions include pregnancy category C with fetal risk revealed in studies in animals, but not established or not studied in humans. It may be used if benefits outweigh the risk to the fetus. Local irritation may occur at application sites including redness, itching, and burning. It is evidence category 1C.

5-Fluorouracil (Efudex) is a topical antineoplastic chemotherapeutic agent that inhibits cell growth and proliferation and is primarily used to treat actinic keratoses and superficial basal cell carcinomas. It has been reported to be effective as an off-label use in treating warts, when used under occlusion and has been more successful in treating flat warts than plantar and common nongenital warts. Dosing in adults is application of the 5% solution or cream daily for up to 1 month. It may be used under occlusion,

but risk of irritation increases. Pediatric usage is not established. There has been no reported drug interactions used topically. Contraindications include documented hypersensitivity and breastfeeding. Precautions include pregnancy category X, contraindicated, and benefit does not outweigh risk. Moderate to severe skin irritation may occur locally. It is category 2B.

Podophyllotoxin (Podofilox) is a purified ingredient of podophyllin and is less irritating than podophyllum resin (see below). Podophyllin is a cytotoxic compound that tends to work better on mucosal surfaces and is used more commonly in the treatment of genital warts (see Chapter 21). Podophyllotoxin is available by prescription and can be applied by the patient at home. Dosing in adults and children of the 0.5% purified solution is that it may be applied topically bid for 3 consecutive days, repeat weekly, not to exceed 4 weeks. Little information is available regarding using it to treat nongenital warts. There are no reported drug interactions. Contraindications are documented hypersensitivity and prolonged use in diabetics and those with impaired circulation. Do not use on nevi or birthmark, do not use on irritated skin or infected skin. It is pregnancy category X, contraindicated and benefit does not outweigh risk. There is insufficient information for rating in an evidence class at this time.

Tretinoin (Retin-A) is a topical retinoic acid that primarily is used to treat acne. It has been successful in off-label use in treating flat warts. It is applied topically daily. Contraindications include documented hypersensitivity and breastfeeding. Precautions include pregnancy category X, contraindicated, and benefit does not outweigh risk. Mild to moderate skin irritation may occur locally. There is insufficient information for rating in an evidence class at this time.

Cidofovir (Vistide) is an antiviral agent used for the treatment of cytomegalovirus infection in HIV patients. It is a nucleotide analog that inhibits viral DNA polymerase and induces apoptosis. Currently it is only available for IV administration to HIV patients for treatment of cytomegalovirus infection. A topical gel has been evaluated in clinical trials for use in treatment of HPV infection. In two patients with recurrent persistent nongenital warts in whom multiple standard therapies were not responsive, the warts resolved using topical cidofovir gel applied 1-2 times per day.³⁷ This remains an investigational drug for warts.³⁸ Dosages in adults and children are not established. Interactions and contraindications other than documented hypersensitivity with topical use have not been established. Precautions include pregnancy category C with fetal risk revealed in studies in animals but not established or not studied in humans. Other precautions for topical use have not been determined. Intralesional injection used to treat nongenital warts has also been proposed. There is insufficient information for rating in an evidence class at this time.

Topical Agents for In-Office Use

Contact sensitizers that induce allergic contact dermatitis, causing a localized inflammation and immune response, may induce wart resolution. Dibutyl squaric acid, also known as squaric acid dibutyl ester (SADBE), and diphen-cyclopropenone (DCP) are contact sensitizers that are not mutagenic/carcinogenic. Dinitrochlorobenzene (DNCB) is a contact sensitizer that is mutagenic according to the Ames test and possibly carcinogenic and should be avoided as when dealing with a potential oncogenic type of wart virus. Older RCT studies with DNCB showed DNCB to be more than twice as effective as placebo.¹⁵ None of these contact sensitizers are FDA approved for medical use and are considered experimental. Apply topical solution to adult or child older than 12 in a light-shielded accessible location such as the inner upper arm to achieve initial sensitization, then apply to warts every 1 to 4 weeks as needed until wart resolves. For SADBE typically a 4% solution is used for sensitization and a 4% or 1% solution is applied topically to the wart. There are no reported drug interactions. Contraindication is documented hypersensitivity. Precautions include pregnancy category C with fetal risk revealed in studies in animals but not established or not studied in humans. It may be used if benefits outweigh the risk to the fetus. Erythema and pruritus occur at treated sites, and occasionally allergic contact dermatitis may be severe (blistering) or rarely become disseminated. Recall dermatitis may occur commonly at the initial sensitization site. Regional lymphadenopathy may occur. DNCB is evidence category 1B, and SADBE and DCP are evidence category 1C.

Podophyllum resin (Podocan-25) is a resin extract derived from *Podophyllum peltatum*, the mayapple plant that contains several cytotoxic compounds. It has a powerful irritant effect and must be used with caution. It works better on mucosal surfaces than keratinized surfaces and is therefore, more commonly used for treatment of genital warts (See Chapter 21). Trained personnel must apply it topically in adults and children because of adverse effects and oral toxicity. It may be left on skin for 1-6 hours before washing off. There are no reported drug interactions. Contraindications are documented hypersensitivity, prolonged use in diabetics and those with impaired circulation, do not use on nevi or birthmarks, do not use on irritated skin or infected skin. It is pregnancy category X, contraindicated, and the benefit does not outweigh the risk. Other precautions include, that podophyllin may cause significant irritation, local erosion, ulceration, and scarring. Systemic side effects of excessive absorption may include fever, nausea, vomiting, confusion, coma, ileus, renal failure, paresthesias, polyneuritis, and leucopenia. Avoid extensive application because of risk of systemic absorption. It is category 1C, with no RCT supporting its effectiveness for nongenital skin.

Cantharidin (Canthacur) is a dried extract of blister beetle (Spanish fly) 0.7% solution in flexible collodion. Dosing in adults and children is to apply sparingly with the wood end of a cotton-tipped applicator in the physician's office, and allow area to be completely dry. Tape occlusion after application can enhance penetration in large or plantar warts, but should be used with caution. Cantharidin causes epidermal necrosis and blistering. Repeat applications at 3 to 4 week intervals may be required. There are no reported drug interactions. Contraindications include documented hypersensitivity. It should not be used near the eyes. Precautions include pregnancy category C with fetal risk revealed in animal studies but not established or not studied in humans. It is a strong vesicant and should be used with caution in intertriginous areas because of possible smearing or occlusion. Adverse effects include blistering, epidermal necrosis at sites of application, and possible "ring wart phenomenon" in which virus is spread circumferentially in adjacent tissue damaged by the treatment process. It is evidence class 2B.

Aminolevulinic acid (Levulan Kerastick) is a photosensitizer that is approved for actinic keratoses and has been successfully used topically off-label in combination with blue light to treat flat warts.³⁹ Several RCT studies on other nongenital warts have produced conflicting results.¹⁵ The main adverse events have been burning pain during and mild discomfort following the treatments. There are no reported drug interactions. Precautions include pregnancy category C with no animal or human data. Photosensitivity occurs after application and before blue light treatment. It is evidence category 2B.

Trichloroacetic acid (Tri-Chlor) is a caustic compound that causes immediate superficial tissue necrosis. It is available as 80% solution that for adults is painted onto lesions in the office after excess keratotic debris is pared. Repeat therapy is performed weekly as needed until the wart resolves. Pediatric use is not established. There are no reported drug interactions. Contraindications include documented hypersensitivity and prolonged use in diabetic persons and those with impaired circulation. Do not use on nevi or birthmarks, face, or mucous membranes. Do not use on irritated skin or infected skin. Precautions include pregnancy category C with fetal risk revealed in studies in animals but not established or not studied in humans. It may be used if benefits outweigh the risk to the fetus. Application may cause pain, burning, and ulceration. If not applied carefully, destruction with resultant scarring of normal surrounding skin may occur. There is insufficient information for rating in an evidence class at this time.

Intralesional Injections

Intralesional immunotherapy off-label using injections of *Candida*, mumps, or *Trichophyton* skin test antigens has been shown to be effective in the treatment of warts,

with reports of success in up to 74% of patients.⁴⁰ A small amount of the antigen is injected intralesionally at the base of the wart every 2-4 weeks until resolution. It is variably effective, evidence class 2C.

Bleomycin (Blenoxane) is an antineoplastic cytotoxic polypeptide chemotherapeutic agent that inhibits DNA synthesis in cells and viruses. It has affinity for HPV-infected tissue and induces vascular changes that result in epidermal necrosis. Bleomycin has been beneficial in treating resistant warts. It is recommended to be held in reserve as a third-line treatment when standard therapies have failed. Wart resolution rates have ranged from 33-92%.^{41,42} In adults the treatment involves injecting 0.5-1 U/mL of the solution directly into the wart, not to exceed 1.5 U/treatment. This treatment is usually painful. Less painful administration involves placing 1 mg/mL drop onto the wart and pricking it into wart with a needle. Pediatric usage is not established. Interactions are unlikely when small amounts are injected intralesionally. Contraindications include documented hypersensitivity and breastfeeding. Precautions include pregnancy category D with fetal risk shown in humans, not recommended in pregnancy. It may cause pain with injection, local urticaria, vaso-occlusive phenomenon (Raynaud phenomenon) with possible distal necrosis of the digit. Permanent damage to nail matrix may occur when used periungually. It may cause mutagenesis and pulmonary toxicity (10%). Idiosyncratic reactions similar to anaphylaxis (1%) may occur, so it is important to monitor for adverse effects during and after treatment. Bleomycin is evidence class 2A.

Interferons alfa-2a and alfa-2b (Roferon and Intron A) are naturally occurring cytokines with antiviral, antibacterial, antitumor, and immunomodulatory actions; intralesional administration is more effective than systemic administration and associated only with mild flulike symptoms. Treatments may be required for several weeks to months before beneficial results are seen. Consider this treatment as third line, and reserve it for warts resistant to standard treatments. Cure rates of 36-63% have been reported. In adults it is injected directly into warts up to 3 times a week for 3-6 weeks. Pediatric dosing is not established. Interactions are minimal with the small amounts injected. Contraindications include documented hypersensitivity. It is to be used with caution in patients with brain metastases, severe hepatic or renal insufficiencies, seizure disorders, multiple sclerosis, or compromised CNS. Precautions include pregnancy category C with fetal risk revealed in studies in animals but not established or not studied in humans. It may be used if benefits outweigh the risk to the fetus. Transient flulike symptoms may occur after initial injections, although tolerance usually develops. Pain at injection sites may occur. Interferon alfa is evidence class 2B.

Systemic Agents

Cimetidine is a type-2 histamine receptor antagonist commonly used to treat peptic ulcer disease. Because of its

immunomodulatory effects at higher doses, cimetidine was considered a possible treatment for warts. However, study results have varied. Double-blind placebo-controlled studies have shown no benefit.⁴³ Dosing in adults and children is 20-40 mg/kg orally per day in divided doses every 6 hours, not to exceed 2400 mg/day. Drug interactions include that it can increase blood levels of theophylline, warfarin, tricyclic antidepressants, triamterene, phenytoin, quinidine, propranolol, metronidazole, procainamide, and lidocaine. Multiple potential drug interactions exist (see full prescribing information for more details). Contraindication is documented hypersensitivity. Precautions include pregnancy category B with fetal risk not confirmed in studies in humans but shown in some studies in animals. Serious reactions may include neutropenia, thrombocytopenia, agranulocytosis, and anemia. Common reactions include headache, nausea, vomiting, diarrhea, and rash. Older patients may experience confusional states. It may cause impotence and gynecomastia in young males. It may increase levels of many drugs. The dose should be adjusted or discontinued if changes in renal function occur. It is evidence class 3B for warts.

Cidofovir (Vistide) is an antiviral agent used for the treatment of cytomegalovirus infection in HIV patients. It is a nucleotide analog that inhibits viral DNA polymerase and induces apoptosis. Currently, it is only available for IV administration to HIV patients for treatment of cytomegalovirus infection. Two reports have described off-label intravenous cidofovir used for the treatment of extensive, disfiguring, and refractory warts in immunocompromised patients. This should be used with caution because of the risk of nephrotoxicity.^{37,44} Contraindications include hypersensitivity and elevated creatinine levels. Warnings include nephrotoxicity as well as neutropenia. Precautions include pregnancy category C with fetal rat low weight and fetal rabbit malformations but fetal risk has not been confirmed in humans. It should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus. It may cause decreased ocular pressure, anterior uveitis/iritis, or metabolic acidosis. There is insufficient information for rating in an evidence class at this time.

Isotretinoin (Accutane) is a synthetic 13-*cis* isomer of the naturally occurring tretinoin (*trans*-retinoic acid), structurally related to vitamin A. It is approved for severe nodular acne but has also been helpful off-label in certain keratinization disorders. It may help off-label with extensive disabling hyperkeratotic warts in immunocompromised patients. It may help alleviate the pain related to the hyperkeratosis and facilitate the use of other treatments. Retinoids also have helped reduce the number of wart lesions in immunosuppressed renal transplant patients. The limiting side effects include liver function abnormalities, increased serum lipid levels, and teratogenicity. A US Food and Drug Administration mandated registry called iPLEDGE is now in place for all individuals prescribing, dispensing, or taking isotretinoin. This registry aims to further decrease the risk of pregnancy and other unwanted

and potentially dangerous adverse effects during a course of isotretinoin therapy. Dosage for adults and children older than 12 is 0.5-2 mg/kg/day orally divided into two doses and taken with food. Drug interactions include toxicity that may occur with vitamin A or acitretin coadministration. Pseudotumor cerebri or papilledema may occur when coadministered with tetracyclines. Reduced plasma levels of carbamazepine may occur. Contraindications include documented hypersensitivity, pregnancy, breastfeeding, paraben sensitivity, or history of psychiatric disturbance. Precautions include pregnancy category X, contraindicated and benefit does not outweigh risk. Common reactions include dry skin, cheilitis, photosensitivity, hypertriglyceridemia, hair loss, and decreased night vision. Inflammatory bowel disease may occur. It may be associated with development of hepatitis. Diabetics may experience problems in controlling blood glucose while on therapy. It is to be discontinued if rectal bleeding, abdominal pain, or severe diarrhea occurs. Use with caution if there is a history of depression or other psychiatric disorder. It is associated with severe birth defects, so females must use two forms of birth control throughout therapy and pregnancy tests must be checked monthly. There is insufficient information for rating in an evidence class at this time.

Surgical Care

Cryosurgery⁴⁵ with liquid nitrogen (-196°C) is the most effective method of cryosurgery. Less cold cryosubstances generally do not achieve sufficient freezing of tissue. It is best to apply liquid nitrogen using a cotton bud applicator or cryospray including the recommended 1-2 mm rim of normal skin tissue around the wart. Repeat every 1-4 weeks for approximately 3 months, as needed. Warn patients about pain and possible blistering after treatment. Use with caution on the sides of fingers, since it can injure underlying structures and nerves. Other side effects may include scarring, ulceration, or hypopigmentation. Wart resolution rates of 50-80% have been reported. Paring the wart, in addition to two freeze-thaw cycles, has been a valuable adjunct to cryosurgery for plantar warts.⁴⁶ It is evidence category 2A.

Lasers are an expensive treatment and are reserved only for large or refractory warts. Multiple treatments may be required. Local or general anesthesia may be necessary. A potential risk of nosocomial infection also exists in health care workers, since HPV can be isolated in the smoke plume and can be inhaled.⁴⁷ Carbon dioxide lasers have successfully treated resistant warts, but the procedure can be painful and leave scarring. One retrospective study revealed a cure rate of 64% at 12 months with carbon dioxide lasers.⁴⁸ The flashlamp-pumped pulse dye laser has shown mixed results in treating warts, with decreased risk of scarring and transmission of HPV in the smoke plume.⁴⁹ The Nd:YAG laser may be used for deeper, larger warts. Laser treatments are evidence category 2B.

Electrodesiccation and curettage may be more effective than cryosurgery, but it is painful, more likely to scar, and HPV can be isolated from the plume. There is insufficient information for rating in an evidence class at this time.

Surgical excision should be avoided in most circumstances because of the risks of scarring and recurrence. There is insufficient information for rating in an evidence class at this time.

CONCLUSIONS

The methods and scientific quality of the reviewed trials are quite variable. There is good evidence that topical treatments containing salicylic acid have a therapeutic effect on nongenital warts. Weaker evidence supports the use of hypnosis for resolution of warts. Resolution rates with placebo preparations are variable but nevertheless considerable. For most other treatment modalities, there is a considerable lack of evidence on which to base rational treatment for nongenital warts. The efficacy of cryotherapy is roughly equivalent to the efficacy of simpler and safer treatments such as topical salicylic acid. The benefits and risks of most of the treatments remain to be determined by future research in the form of RCT. Adequate funding of such trials remains a chronic issue.

What We Know

- Treatment of warts can be difficult. Warn patients that multiple treatments often may be required. The patient must build a CMI response against the wart virus to obtain resolution.
- Salicylic acid topical treatment of nongenital warts is moderately efficacious. Warn patients that treatments may result in pain, irritation, blistering, ulceration, and even scarring. Cryosurgery can also be efficacious, but with associated pain and risk of scarring or hypopigmentation. Other methods are of lower proven efficacy. See Table 22-1.
- Perform surgical removal of warts with caution, because an increased risk of scarring exists, without an increased rate of wart resolution.
- If a wart is extremely large and resistant to conventional therapies, consider an incisional biopsy to rule out the diagnosis of verrucous carcinoma, a rare, slow growing, low-grade, well-differentiated carcinoma that most commonly occurs on the plantar surface and can become deeply invasive. Metastases are rare. Verrucous carcinoma can easily be misdiagnosed as a common wart, because the two share similar clinical and histologic characteristics.
- No vaccine is currently available for non-genital warts.

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Treatment of Herpes Simplex

23

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INTRODUCTION

Herpes simplex viruses cause intermittently recurring mucocutaneous vesicular eruptions. These commonly encountered human DNA pathogens usually replicate in the skin and mucosa and then infect the nerve endings. The virus then ascends to ganglia, where it remains during latency until reactivation. Of the two types, HSV-1 is most commonly associated with orofacial lesions, while HSV-2 is mostly associated with genital pathology. However, both viruses can cause infections in either area. Herpes viruses can also infect noncutaneous organs including ocular tissue or the CNS. HSV is also an important risk factor for acquisition and transmission of HIV.

EPIDEMIOLOGY

Worldwide, genital herpes is the most common sexually transmitted disease. An estimated 40–60 million persons in the United States have a history of genital herpes infections, and new infections occur at a rate of approximately 500,000 to 1 million per year.¹ Because of lack of awareness and frequent recurrence, many transmissions occur by asymptomatic shedding. HSV-1 seropositivity is common amongst the adult population and infections are commonly acquired in childhood. HSV-2, however, is correlated with sexual behavior, and is therefore usually acquired in adolescence and adulthood.

SEARCH METHODOLOGY

Literature searches for randomized controlled trials, meta-analyses, and reviews were conducted. Final reviews included studies published through February 2010. Both Cochrane Central Register of Controlled Trials (key words: herpes labialis, herpes genitalis) and PUBMED (search terms: herpes labialis, herpes simplex, herpes genitalis, herpes suppression, herpes treatment) were used in searches. To be included, studies were evaluated for feasibility in treatment options, degree of efficacy, and reasonable evaluations of commonly accepted treatment options.

Background-Treatment of HSV

Acyclovir

The advent of acyclovir in herpes treatment is still considered one of the most important advances in antiviral therapy. While first developed as a possible anticancer drug, its use for inhibition of viral activity, specifically against herpesviridae, was evident early on. Extensive literature has been published confirming its high clinical efficacy.

Since its arrival three decades ago, its mechanism of action has been the prototype in antiviral drug development. Acyclovir is a synthetic acyclic purine nucleoside analogue; it is converted to its active compound by a viral encoded tyrosine kinase to a monophosphate derivative. This event makes it a selective inhibitor for HSV-infected cells. It is then phosphorylated by cellular kinases to the active compound. This molecule is concentrated up to 100 times higher in infected cells compared to those uninfected. Acyclovir triphosphate then competes with deoxyguanosine triphosphate for viral DNA synthesis. As the active compound lacks the 3' hydroxyl group needed for DNA elongation, the viral DNA polymerase is inactivated when the chain terminates with the addition of acyclovir triphosphate. Selective action for viral replication versus host DNA replication is conferred, as the viral DNA polymerase has a greater affinity for activated acyclovir over host DNA polymerase.²

Acyclovir was originally tested and marketed as a topical and IV medication for use in treatment of susceptible herpesviridae infections. Steady state peak levels of IV doses every 8 hours of 5 mg/kg is 9.9 pg/mL and of 10 mg/kg is 20 pg/mL. To enhance patient compliance and ease administration, an oral form was produced. Although bioavailability was compromised, increased oral dosing regimens of 200 mg and 800 mg produced acceptable steady state peak levels of 0.57 ug/mL and 1.57 ug/mL, respectively. Acyclovir is minimally metabolized and is excreted 85% in its original state by glomerular filtration and tubular secretion. Therefore, renal dosage adjustments may be necessary. In patients with normal renal function, acyclovir has a half-life of 2 to 3 hours.³

Within the herpesviridae family, acyclovir is an effective therapeutic regimen for a host of viruses because of its selective mechanism of action. Evaluating activity with average inhibitory concentration 50, acyclovir is most active against HSV-1 (at 0.04 ug/mL). HSV-2 requires 0.10 ug/mL, and VZV 0.50 ug/mL for effective antiviral activity.⁴ Because of its very high efficacy with herpes simplex viruses, acyclovir has been the most widely prescribed antiviral therapy for acute and recurrent episodes since its introduction.

What is the Role of Medications in Therapy for Primary Therapy in Herpes Labialis Infections?

Treatment in herpes labialis has historically been challenging because of the high rates of recurrence. Patients have been treated with a wide variety of topical and oral applications including zinc oxide/glycine cream, antiviral cream, anesthetic cream, heat therapy, and oral antivirals. Patients treated with topical acyclovir cream in a randomized double blind controlled study experienced a mean duration of episodes of 4.3 days compared to 4.8 days for those treated with the vehicle control (hazards ratio [HR] = 1.23; 95% confidence interval [CI], 1.06 to 1.44; P = 0.007). There was a statistically significant reduction in the duration of lesion pain and efficacy was evident whether therapy was initiated “early” (prodrome or erythema lesion stage) or “late” (papule or vesicle stage).⁵ Another earlier double-blind, placebo controlled, randomized studies found a significant reduction in the duration of vesiculation from 2.7 to 1.8 days (P = 0.016) and in the total healing time from 8.3 to 5.7 days (P = 0.022) on topical acyclovir.⁶ This may be explained by time of initiation of therapy and the degree of penetration of vehicle used.

Penciclovir, which has a similar mechanism of action to acyclovir, was used in another study in a cream-based application. The multicenter placebo-controlled study reported several clinical endpoints. Healing of classic lesions (vesicles, ulcers, and/or crusts) was 0.7 day faster for penciclovir-treated patients compared with those who received vehicle control cream (median, 4.8 days vs 5.5 days; hazard ratio [HR], 1.33; 95% confidence interval [CI], 1.18-1.49; P<.001). Pain (median, 3.5 days vs 4.1 days; HR, 1.22; 95%

CI, 1.09-1.36; P<.001) and lesion virus shedding (median, 3 days vs 3 days; HR, 1.35; 95% CI, 1.10-1.64; P=.003) also resolved more quickly for penciclovir-treated patients compared to patients who applied the vehicle control. The efficacy of penciclovir cream was apparent when therapy was initiated in early or late stages.⁷ However, acyclovir cream is usually more practical as penciclovir must be applied every 2 hours during the day. Another topical agent is docosanol, a compound with a unique mechanism of action involving viral fusion inhibition. In randomized, clinical trials, a 10% docosanol cream formulation, initiated within 12 hours of symptom onset, demonstrated efficacy in reduction of time-to-healing compared with a polyethylene glycol control.⁸ Because of its great safety profile and ease of use, it is the first topical antiviral approved for over-the-counter use in recurrent herpes labialis.

Because of the cumbersome use of topical medications, patients sometimes prefer oral therapy with antiviral medications. Early double-blind, randomized, patient-initiated clinical studies with oral acyclovir showed the mean duration of pain was reduced by 36% (P = .02) and the mean healing time to loss of crust by 27% (P = .03) in the treatment group.⁹ In one study, patients with herpes labialis were instructed to use study medications at the first symptom of an outbreak; findings indicated 1-day valacyclovir treatment regimen for oral HSV is safe and effective.¹⁰ It has also been shown that single-dose famciclovir reduced time to healing of herpes labialis lesions by approximately 2 days compared with placebo¹¹ (Table 23-1).

Research question and answers:

What Does the Data Indicate Regarding Preventative Treatments for Recurrent Oral Herpes Lesions?

Sun exposures, and most particularly UV rays, have been known to affect the cutaneous immune response. One double-blind, placebo-controlled crossover study found after placebo and UV exposure, herpes labialis developed in 27 (71%) of the 38 patients, in contrast, when sunscreen was applied before UV exposure, no lesions developed, but 1 of the 35 patients shed virus at the exposure site.¹² However, another study with skiers showed application of a sunscreen

TABLE 23-1—Episodic Dosing for Initial Primary Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	15 mg/kg 5 times a day for 7 d	II ^{3,21}	No
Valacyclovir hydrochloride	1 g twice a day for 7 d	V ²²	No
Famciclovir	500 mg twice a day for 7 d	V ²²	No

Abbreviation: FDA, Food and Drug Administration.

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TABLE 23-2—Intermittent Episodic Therapy or Recurrent Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	400 mg 5 times a day for 5 d	II ²³	No
Valacyclovir hydrochloride	2 g twice a day for 1 d	I ²⁴	Yes
Famciclovir	Three 500-mg tablets as a single dose	I ^{10,25}	Yes
Topical therapy			
Penciclovir cream, 1%	Apply every 2 h during waking hours for 4 d	I ²⁶⁻²⁸	Yes
Acyclovir cream, 5%	Apply 5 times a day for 4 d	I ^{27,29}	Yes

Abbreviation: FDA, Food and Drug Administration.

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with a sun protection factor (SPF) of 15 failed to influence the reactivation rate as compared with a placebo.¹³ More research may be needed to discern the benefits of sunscreen in preventing relapse of herpes outbreaks.

Topical acyclovir cream therapy was studied in skiers who had experienced more than three episodes of sun-induced herpes labialis during the previous year. The acyclovir group had significantly fewer lesions ($p <0.01$) than the placebo group (21% vs. 40%) during the 4-day follow-up period.¹⁴ Two other similar trials sought to study the long-term effects with application of prophylactic acyclovir cream, which was applied 2 or 4 times a day for 16 weeks.¹⁵ Only the 4 times a day application showed minor differences in number of days with lesions (acyclovir group: 9.5 days; placebo group: 12.4 days) and symptoms (acyclovir group: 12.2 days; placebo group: 17.4 days).¹⁶ Because of the small benefits, this therapy may not justify the impracticality of frequent applications through the day.

In one study, only 7% of patients treated prophylactically with oral acyclovir developed lesions compared to 26% with placebo during observation on their ski holidays.¹⁷ Additionally, double-blind, placebo-controlled studies with valacyclovir have also yielded encouraging results, 60% in a valacyclovir group compared to only 38% in a placebo group were recurrence-free throughout the

4-month treatment period ($P=.041$). The mean time to first recurrence was significantly longer with valacyclovir (13.1 weeks) compared with placebo (9.6 weeks) ($P=.016$). The total number of recurrences in patients using valacyclovir was 24 compared with 41 in patients using placebo¹⁸ (Tables 23-2 and 23-3).

What is the Role of Medications in Therapy for Primary Herpes Genitalis Infections?

Oral acyclovir therapy, being nearly as effective as IV, but with easier administration has been the drug of choice in primary and recurrent episodes of genital herpes. Despite its use, acyclovir seems to be much more effective on the primary infection compared to subsequent recurrences. In one of the first studies of the drug, subjects were randomized to receive either placebo or acyclovir (200 mg per dose) five times daily for 10 days. Compared to placebo, acyclovir treatment significantly reduced virus shedding, new lesion formation after 48 hours, and the duration of genital lesions in both men and women. The total duration and severity of clinical symptoms (such as pain, adenopathy, dysuria, and malaise) were significantly reduced by acyclovir in both men and women by the third and fourth

TABLE 23-3—Chronic Suppressive Therapy for Labial Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved
Acyclovir	400 mg twice a day	II ⁸	No
Valacyclovir hydrochloride	500 mg once a day 1 g once a day	II ⁹ II ⁶⁶	No No
	500 mg twice a day ^a		
Famciclovir	500 mg twice a day	V ⁶⁷	No

Abbreviation: FDA, Food and Drug Administration.

^aHuman immunodeficiency virus-positive patients.

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day, respectively ($P < 0.025$).¹⁹ Another double-blind, placebo-controlled study showed that primary genital herpes patients treated with acyclovir had shorter median duration of viral shedding (2 days), time to crusting of all lesions (7 days), time to healing of all lesions (12 days), and duration of local pain (5 days) and constitutional symptoms (3 days) were shorter than among placebo recipients (9, 10, 16, 7, and 6 days, respectively).²⁰ In efforts to try to find more efficacious treatment regimens, one study compared whether receiving higher (4 g) than standard (1 g) daily dose of oral acyclovir had a significant effect on clinical outcomes. There was no statistically significant difference in the duration of symptoms or viral shedding between the two dose groups, nor did the median time to first recurrence differ between the two groups. Also noteworthy was that adverse gastrointestinal effects developed in 8% of subjects receiving the higher dose, whereas no adverse reactions were observed among those receiving the standard dose ($P = 0.10$).²¹

Because of the frequent dosing regimen of acyclovir, many patients may not be completely compliant, and therefore may not maintain therapeutic drug levels. As such, valacyclovir is available for once daily dosing and even has shown higher absorption rates. In international, multicenter, double-blind, randomized clinical comparison trials, valacyclovir and acyclovir did not differ significantly in efficacy with respect to duration of viral shedding (HR, 1.00; 95% CI, 0.84-1.18), time to healing (HR, 1.08; 95% CI, 0.92-1.27), duration of pain (HR, 1.0; 95% CI, 0.85-1.18), and time to loss of all symptoms (HR, 1.02; 95% CI, 0.85-1.22).²² Valacyclovir has been approved for primary genital herpes therapy at a dosage of 1000 mg BID for 10 days.

Another oral medication with the similar mechanism of action, famciclovir, is metabolized to penciclovir, which is active against herpes virus. In the treatment of primary genital HSV, famciclovir has been shown to have equal efficacy to acyclovir at a dose of 250 mg 3 times a day for 5 to 10 days. Also the effects of famciclovir 125, 250 or 500 mg 3 times daily for 10 days were not significantly different from acyclovir 200 mg 5 times daily for 10 days.²³ No significant differences in times to cessation of viral shedding, complete healing, or loss of all symptoms was observed between the two groups in these studies. Again,

reduced administration frequency is a practical advantage over acyclovir (Table 23-4)

What Are the Evidence-Based Treatments for Recurrent Herpes Genitalis?

As stated before, acyclovir remains the prototypical drug for HSV genitalis infections. Topical 5% acyclovir in polyethylene glycol ointment decreased the duration of viral shedding but had no significant clinical benefits. However, although there is a statistically significant benefit to using oral acyclovir in genital herpes recurrence, it shortens the duration of viral shedding and time to healing (6 days down from 7 without therapy), when initiated within the first 24 hours of onset. Other symptoms, such as pain, itching, and time to next episode are not affected.²⁴ These results indicate that most patients have limited clinical improvement for episodic treatment of recurrent genital herpes.

Another study, which sought to compare valacyclovir and acyclovir episodic therapy in recurring herpes attacks showed better outcomes, though still marginal. Patients self-initiated oral therapy with 1000 mg of valacyclovir hydrochloride twice daily, 200 mg of acyclovir 5 times daily, or placebo for 5 days. Both drugs were significantly more effective than placebo in speeding resolution of herpetic episodes (median duration, 4.8, 4.8, and 5.9 days, respectively); the hazards ratios for valacyclovir and acyclovir vs. placebo were 1.66 (95% CI, 1.38-2.01) and 1.71 (95% CI, 1.41-2.06) (both $P < .001$) respectively. Similarly, valacyclovir and acyclovir significantly hastened lesion healing (HR vs. placebo 1.88 [95% CI, 1.53-2.32] and 1.90 [95% CI, 1.55-2.34], respectively; $P < .001$). Pain duration was shorter in valacyclovir and acyclovir-treated patients (median, 2 vs. 3 days). Viral shedding stopped faster in patients treated with valacyclovir or in patients treated with acyclovir (2.25, 2.24 times respectively) versus placebo. Aborted episodes, in which lesions did not progress beyond the macule or papule stage, were increased in patients treated with valacyclovir (25.9%) or acyclovir (24.8%) versus placebo (19.8%). Valacyclovir and acyclovir did not differ significantly with regard to their respective effects on any of the above parameters.²⁵

TABLE 23-4—Episodic Dosing for Initial Primary Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	400 mg 3 times a day for 7–10 d 200 mg 5 times a day for 7–10 d	V ^{38–41} I ^{38,40}	No Yes	Yes Yes
Valacyclovir hydrochloride	1 g twice a day for 7–10 d	I ⁴⁰	Yes	Yes
Famciclovir	250 mg 3 times a day for 5–10 d	I ^{42,43}	No	Yes (10-d regimen)

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

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TABLE 23-5—Intermittent Episodic Therapy for Recurrent Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	200 mg 5 times a day for 5–10 d	I ^{41,44,45,53}	Yes	No
	400 mg 3 times a day for 5 d	V	No	Yes
	400 mg 3 times a day for 5–10 d ^a	V	No	Yes
	800 mg twice a day for 5 d	II ⁴⁶	No	Yes
	800 mg 3 times a day for 2 d	II ⁴⁷	No	Yes
Valacyclovir hydrochloride	500 mg twice a day for 3 d	I ⁴⁹	Yes	Yes
	1 g twice a day for 5–10 d ^a	II ⁵⁴	No	Yes
	1 g once a day for 5 d	I ⁴⁸	No	Yes
Famciclovir	125 mg twice a day for 5 d	I ^{51,52}	No	Yes
	500 mg twice a day for 5–10 d ^a	II ⁵⁵	Yes (7-d regimen)	Yes
	1 g twice a day for 1 d	I ¹⁴	Yes	Yes

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

^aFor human immunodeficiency virus-positive patients, suggested regimens were derived from studies of patients with genital herpes. However, we expect these treatments to also be useful for patients with labial herpes.

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Famciclovir has been shown to be significantly more effective than placebo in treatment of recurrent episodes of genital herpes when taken at 125, 250, or 500 mg doses BID for 7 days. When initiated within the first 6 hours of symptoms, famciclovir significantly reduced the time to healing, the time to cessation of viral shedding, and duration of lesion edema. This treatment also significantly reduced the symptoms of pain, burning, tenderness, and tingling.²⁶ Therefore, famciclovir is effective for acute episodic treatment of recurrent genital herpes and provides the convenience of twice-daily administration (Table 23-5).

What Are the Evidence-Based Treatments for Herpes Simplex II?

Suppressive therapy with oral acyclovir is very effective in reducing recurrences of genital herpes by up to 80%. Successful suppressive therapy may be achieved with lower levels of drug dosing and patients may need titration to discern the minimum dose required. Reassessment of need for suppression may be performed every 12 months.³

In one early trial, adults with six or more episodes of genital herpes in the previous year were enrolled in a 1-year, multicenter, double-blind trial, comparing placebo with 400 mg of acyclovir administered orally twice daily. Patients with episodes during the study were treated with 200 mg of acyclovir administered orally five times daily for 5 days; this allowed comparison of suppressive and episodic treatment. After 1 year, 44% versus 2% of patients (suppressing and placebo/episodic respectively) remained free of recurrences, and the mean numbers of recurrences per year were 1.8 and 11.4, respectively. There was no evidence of substantial adverse effects, and therefore successful suppression can be maintained for extended periods.²⁷ One study showed that resistance to acyclovir

of herpes simplex virus was not observed over 5 years of treatment. It also reported maintenance of efficacy and of good safety profiles, further expanding treatment longevity.²⁸ Similar trials with acyclovir suppression at various dosage regimens have shown the utility of antiviral therapy in avoiding recurrent outbreaks.

Valacyclovir also showed promising results in suppressive therapy with an easier regimen. In an international, randomized, double-blind, placebo-controlled suppression study, 500 mg daily of valacyclovir significantly prolonged the time to first recurrence of HSV-2 genital herpes in newly diagnosed subjects compared to placebo, with approximately 43% of subjects on placebo and 71% of subjects on valacyclovir recurrence-free at 24 weeks ($P < 0.001$). It also reduced the mean number of genital HSV-2 recurrences per month during the 24-week study period (0.11 for valacyclovir, 0.48 for placebo, $P < 0.001$).²⁹ In another study to discern dosing regimens, patients were randomized to receive valacyclovir (250 mg, 500 mg, or 1 g once daily, or 250 mg twice daily), acyclovir (400 mg twice daily), or placebo, for 1 year. There was a dose-response relationship ($P < .0001$) across the once-daily valacyclovir regimens, and twice-daily valacyclovir and acyclovir were similar in effectiveness. In patients with less than 10 recurrences per year, valacyclovir 500 mg once daily was sufficient for suppression. One gram of valacyclovir once daily, 250 mg of valacyclovir twice daily, or 400 mg of acyclovir twice daily were more effective in patients with 10 or more recurrences per year.³⁰

Famciclovir suppressive treatment for genital herpes recurrence was approved at a dose of 250 mg BID. The first of two multicenter, double-blind, placebo-controlled studies demonstrated the median time to first recurrence was 82 days versus 114 days in placebo compared to those receiving 125 mg of famciclovir once a day. The time to the first clinical recurrence was significantly prolonged in subjects

who received famciclovir, 125 mg twice daily (HR, 1.8; 95% CI, 1.0-3.0; P=.03), and in those who received famciclovir, 250 mg twice daily (HR, 3.6; 95% CI, 1.9-6.9; P<.001) when compared to placebo. Furthermore, famciclovir 250 mg twice daily, which was found to be the optimal dose, suppressed recurrences in 90% of the treatment group, compared with 48% in the placebo group.²³ The other study showed in an intent-to-treat analysis, famciclovir (125 mg or 250 mg 3 times daily or 250 mg BID) significantly delayed the time to the first recurrence of genital herpes at all dose regimens (HR, 2.9-3.3; P<.001); median time to recurrence for famciclovir recipients was 222 to 336 days compared with 47 days for placebo recipients. Encouragingly, the number of patients without recurrence was approximately 3 times higher in famciclovir recipients (79%-86%) than in placebo recipients (27%) at 6 months (relative risks, 2.9-3.1; P<.001); efficacy was maintained at 12 months.³¹ In both studies, famciclovir was well tolerated with an adverse experience profile comparable to placebo.

Comparative studies given above have shown similar efficacy of acyclovir and valacyclovir. Famciclovir 250 mg BID and valacyclovir 500 mg daily were compared in two randomized, double-blind, placebo-controlled studies. In study 1, first recurrence time was similar in famciclovir and valacyclovir recipients, HR 1.17 (95% CI, 0.78-1.76), but time to first molecularly confirmed recurrence was shorter among famciclovir recipients, HR = 2.15 (95% CI, 1.00-4.60). In study 2, HSV was detected on 3.2% of days among famciclovir recipients and 1.3% of days among valacyclovir recipients, relative risk 2.33 (95% CI, 1.18-4.89).³² Most recently, a meta-analysis was performed, evaluating 14 randomized clinical trials. In antiviral drug groups compared with the placebo, the global relative risk of developing at least one recurrence during the study was reduced by 47% (95% CI 45%-49%). The data also revealed the best regimens which had comparable efficacies; (ie., acyclovir) (400 mg twice daily), valacyclovir (250 mg twice daily), and

famciclovir (250 mg twice daily), or once daily valacyclovir (500 mg)³³ (Table 23-6).

How is Antiviral Therapy Used to Decrease Transmission Rates?

Acyclovir used in infected sexually active patients, can also be used to address concerns for spreading the infection to sexual partners. Earlier studies did not show a decrease in the rate of viral shedding during the asymptomatic phase. However, one study did find a 95% reduction in subclinical shedding while patients were on acyclovir therapy.³⁴ Another study found suppression with acyclovir regimens lead to decreased viral shedding, but not to undetectable levels.³⁵ In an investigation of daily genital secretions taken from infected women, patients were discovered to have 80% reduction in frequency of HSV-2 DNA detection while on acyclovir 400 mg BID; upon discontinuation, patients resumed original levels of shedding.³⁶ A recently published double-blind, three-period crossover trial examined viral shedding with the antivirals valacyclovir and acyclovir against placebo. HSV was detected at least once in 62 (90%) participants by culture and in 68 (98%) by PCR. During placebo, the total HSV shedding rate was 15.4% of days by culture (PCR, 40.2%); the subclinical shedding rate was 6.6% by culture (PCR, 27.1%). Both antivirals were associated with lower HSV shedding by culture (relative risk [RR], 0.03 [95% CI, 0.01–0.07] for valacyclovir and RR, 0.05 [95% CI, 0.03–0.10] for acyclovir) and PCR (RR, 0.18 [95% CI, 0.12–0.26] for valacyclovir and RR, 0.20 [95% CI, 0.15–0.28] for acyclovir), compared to placebo. No significant differences in frequency and quantity of HSV were detected by PCR between the valacyclovir and acyclovir arms.³⁷ These findings are encouraging since decreased viral shedding is a necessary component of a reduced transmission rate.

This may be the mechanism behind decreasing transmission rates in an investigation of discordant couples counseled on safe sex practices. This study found that once

TABLE 23-6—Chronic Suppressive Therapy for Genital Herpes

Antiviral Drug	Dosing Schedule	Level of Evidence	FDA Approved	CDC Recommended
Acyclovir	400 mg twice a day 400-800 mg twice to 3 times a day ^a	I ^{61,69,71,81} I ⁸⁹	Yes No	Yes Yes
Valacyclovir hydrochloride	1 g once a day 500 mg once a day 500 mg twice a day ^a 250 mg twice a day	I ^{81,90} I ^{79,80} I ^{89,91} I ^{61,81}	Yes Yes Yes No	Yes Yes Yes No
Famciclovir	250 mg twice a day 500 mg twice a day ^a	I ^{60,65,82} II ⁸⁷	Yes No	Yes Yes

Abbreviations: CDC, Centers for Disease Control and Prevention; FDA, Food and Drug Administration.

^aHuman immunodeficiency virus-positive patients.

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daily suppressive therapy with valacyclovir reduced the risk of transmission of HSV-2 in heterosexual immunocompetent adult couples discordant for HSV-2 infection. In an 8-month double blind study, daily valacyclovir compared to placebo reduced the risk of acquisition of symptomatic genital HSV-2 infection by 75% (2.2% placebo vs. 0.5% valacyclovir; HR = 0.25; p = 0.008). The overall risk of acquisition of HSV-2 infection (defined via laboratory-confirmed symptoms or seroconversion) was reduced by 48% (3.6% placebo vs. 1.9% valacyclovir HR = 0.52; p = 0.04).³⁸ These results were reinforced with a double-blind randomized trial in which patients were assigned to a 500 mg valacyclovir arm or placebo for 8 months. Of the 743 valacyclovir patients, four developed clinically symptomatic HSV-2 infection, as compared to 16 of 741 who were given placebo (HR, 0.25; 95 percent CI, 0.08 to 0.75; P=0.008). Subclinical infection as detected in an additional 14 of the susceptible partners who received valacyclovir (1.9%), as compared with 27 (3.6%) who received placebo (HR, 0.52; 95 percent CI, 0.27 to 0.99; P=0.04). Seroconversion of genital secretion occurred at the rate of 2.9% of the days among the HSV-2-infected (source) partners who received valacyclovir, as compared with 10.8% of the days among those who received placebo (P<0.001). The mean rates of recurrence were 0.11 per month and 0.40 per month, respectively (P<0.001).³⁹ Based on these studies, another group devised a mathematical model of HSV-2 epidemiology, which included suppressive therapy with the efficacy observed in the clinical trial. The resulting data demonstrated that with coverage rates of 3.2%, the incidence of HSV-2 would be reduced by between 1.8% and 2.8%. Higher coverage rates were estimated to reduce the incidence of new cases up to 13%. It was found that suppressive therapy reduces incidence of HSV-2, and that starting suppression closer to the time of infection reduces the number of new cases.⁴⁰

How are Treatment Regimens Modified for Immunocompromised Patients?

Just as in most fields, many patients are not textbook cases and may present with a myriad of different comorbidities. There have been evident challenges in finding appropriate treatments for people with some degree of compromised immune systems. However, because of the significant reduction in quality of life in these patients, much effort has been placed towards alleviating possible stressors.

For oral herpes, a recent systematic review of 17 trials analyzed preventative interventions. It was found that in placebo controlled trials for the prevention of HSV manifestations, acyclovir was effective when measured by oral lesions or viral isolates (RR = 0.16, 95% CI 0.08 to 0.31 nine trials; RR = 0.17, 95% CI 0.07 to 0.37 nine trials). There was no evidence that higher doses of valacyclovir are more efficacious than lower doses, or that valacyclovir is more effective than acyclovir. Interestingly, in one trial placebo

was found to be more effective than prostaglandin E for prevention of viral isolates (RR = 1.87, 95% CI 1.12 to 3.14). Acyclovir was also found to be effective for the treatment of HSV in terms of duration of viral shedding (median of 2.5 days versus 17.0 days, P = 0.0002; 2 days compared to more than 9, P = 0.0008), time to first decrease in pain (median 3 days compared to 16, P = 0.04), complete resolution of pain (9.9 days compared to 13.6 days, P = 0.01; median of 6 days compared to 16, P = 0.05), 50% healing (median of 6 days compared to 11, P = 0.01) and total healing (median 13.9 days compared to 20.7 days, P = 0.08; median of 8 days compared to 21, P = 0.0).⁴¹

Genital herpes in immunocompromised patients has been studied extensively as well. In one of the first studies, patients received acyclovir at 250 mg/m² intravenously over 1 hour every 8 hours for 7 days or placebo. It was found that acyclovir recipients had significantly shorter periods of virus shedding (p<0.0002) and lesional pain (p<0.01), and more rapid lesion scabbing (p<0.004) and time to healing (p <0.04).⁴² Another study delineated effective regimens of acyclovir 400 mg 5 times a day for 5 days or until the eruption clears and then 400 mg 3 times a day for 1 or 2 months followed by 400 mg twice a day thereafter.⁴³ A study on dosing and alternative treatments revealed that oral valacyclovir is comparable to IV acyclovir in achieving systemic exposure levels. Testing of blood levels showed acyclovir levels after oral valacyclovir 1000 mg and IV acyclovir 5 mg/kg with AUC0-8 (oral/IV ratio = 1.16; 90% CI 0.98-1.39). Oral valacyclovir appears to lead to similar treatment outcomes as IV acyclovir therapy, and offers a convenient, safer, and more cost effective alternative.⁴⁴ Further randomized trials are needed to test the equivalent efficacy of other antivirals to IV acyclovir.

For Severe Manifestations of HSV Infections, What Are the Evidence-Based Treatment Guidelines?

Though primary and recurrent episodes described above can both be treated with oral therapy, severe reactions to infection need regimens that are more aggressive. Intravenous antivirals are the most effective treatment for disseminated herpes outbreak usually leading to a large reduction in symptoms. Patients with serious HSV systemic disease burden, (i.e., disseminated infection, pneumonitis, or hepatitis) or CNS complications (i.e., meningitis or encephalitis) typically need hospitalization for IV treatment. The literature supporting concrete treatment regimens is limited, however, the CDC web site recommends: acyclovir 5–10 mg/kg body weight IV every 8 hours for 2–7 days or until clinical improvement is observed, followed by oral antiviral therapy to complete at least 10 days of total therapy.

Severe manifestations of herpes simplex infection, such as herpes gingivostomatitis and eczema herpeticum,

have sparse data analyzing efficacy of pharmacotherapy pertaining to individual disease states. One randomized-controlled study with herpes gingivostomatitis showed marginally better results in the acyclovir group compared to the placebo group in children <6 years of age in reducing the number of individuals with oral lesions (RR 0.10 (95% CI 0.02 to 0.38), new extra oral lesions (RR 0.04 (95% CI 0.00 to 0.65), difficulty in eating (RR 0.14 (95% CI 0.03 to 0.58), and drinking difficulties (RR 0.11 (95% CI 0.01 to 0.83), however the study design may have been subject to some bias. The other study with 20 patients showed no benefit in the antiviral group compared to placebo. The Cochrane database review on this subject concluded that there was weak evidence to support acyclovir treatment for decreasing some of the symptoms caused by primary herpetic gingivostomatitis.⁴⁵ As such, treatment guidelines supported by effective trials are limited. Most of these infections are treated intravenously with antivirals within dose safety limits based on therapy for primary oral or genital infection regimens.

What Are the Treatment Options for Acyclovir Resistant Herpes Infections?

For the most part, antiviral resistance in herpes simplex infections has not been a major issue in treating HSV infections in immunocompetent patients to date. However, the incidence of acyclovir resistance in immunocompromised patients has been greater (4-7%).⁴⁶ During worldwide clinical trials and surveillance programs for the last 20 years, thousands of HSV isolates have been collected to test for HSV susceptibility to acyclovir or penciclovir. Authors studying these isolates published two consistent findings: (1) The prevalence of acyclovir-resistant HSV is higher in severely immunocompromised patients than in immunocompetent patients; (2) there was no increase in the prevalence of resistant HSV in either immunocompromised or immunocompetent populations during the studied period. Furthermore, through clinical and laboratory experience, with very rare exceptions, acyclovir-resistant mutants do

not appear to be capable of initiating a latent infection that can subsequently be reactivated. Almost all resistant HSV mutants lack the ability to express functional TK and which may account for this phenomenon.⁴⁷

Nevertheless, in these exceptions, as well as severely immunocompromised patients, treatment options have been delineated to address the extent and severity of HSV infection. Foscarnet is a pyrophosphate antagonist that binds to viral DNA preventing pyrophosphate exchange. It does not require phosphorylation, and is therefore active against HSV strains that are resistant to HSV based upon TK variations. In one uncontrolled study, 81% of patients with resistant infection exhibited clinical response to treatment with foscarnet.⁴⁸ Another option is the alternative nucleoside analogs, such as cidofovir, an acyclic nucleoside phosphonate analogue of deoxycytosine monophosphate. Since cidofovir is a nucleotide, it bypasses the first HSV-dependent phosphorylation step required for nucleosides such as acyclovir. A randomized, double-blind, clinic-initiated, sequential dose-escalation pilot study was performed to compare the safety and efficacy of single applications of 1, 3, and 5% cidofovir gel with placebo in the treatment of early recurrent genital herpes. Cidofovir gel at all strengths significantly decreased the median time to negative virus culture in a dose-dependent fashion (3.0 days in the placebo group versus 2.2, 1.3, and 1.1 days in the 1, 3, and 5% cidofovir gel treatment groups, respectively; P = 0.02, 0.0001, and 0.0003, respectively). A trend toward a reduction in the median time to complete healing in association with treatment was present, but the differences were not statistically significant (5.0 days in the placebo group versus 4.3, 4.1, and 4.6 days in the 1, 3, and 5% cidofovir gel treatment groups, respectively).⁴⁹

Additional treatments are available or being tested for future use in HSV treatment, including trifluridine, interferon alpha and beta, lobucavir, cidofovir, edoxudine, and many vaccines aimed at prevention.⁵⁰ However, the risk of adverse events for all alternative therapies, most commonly compromise of kidney function, makes these medications challenging to use.

What We Know

Genital herpes is the most common sexually transmitted disease. 67 million people have genital herpes infection; the annual incidence is 1 million cases per year.

Acyclovir is the prototypical herpesviridae DNA polymerase inhibitor and has selectivity by being activated by viral tyrosine kinase.

Treatment for primary orofacial herpes infection:

- Acyclovir 15 mg/kg 5 times a day for 7 days
- Valacyclovir 1 g BID for 7 days
- Famciclovir 500 mg BID for 7 days

Treatment for episodic orofacial herpes recurrence:

- Acyclovir 400 mg 5 times a day for 5 days

Treatment for primary genital herpes infection:

- Acyclovir 400 mg 3 times a day or 200 mg 5 times a day for 7-10 days
- Valacyclovir 1 g BID for 7-10 days
- Famciclovir 250 mg 3 times a day for 5-10 days

Treatment for episodic genital herpes recurrence:

- Acyclovir 200 mg 5 times a day for 5-10 days

- Valacyclovir 2 g BID for 1 day
- Famciclovir 500 mg 3 tab as single dose
- Penciclovir topical 1% cream applied every 2 waking hours for 4 days
- Acyclovir topical 5% cream applied 5 times a day for 4 days

Suppressive therapy for orofacial HSV disease:

- Acyclovir 400 mg BID
- Valacyclovir 500 mg once a day, 1 g once a day, 500 mg BID (for immunocompromised)
- Famciclovir 500 mg BID

- Valacyclovir 500 mg BID for 3 days
- Famciclovir 125 mg BID for 5 days
- See table for alternative regimens

Suppressive therapy for genital HSV disease:

- Acyclovir 400 mg BID
- Valacyclovir 500 mg or 1 g once a day, 250 mg BID, 500 mg BID (for immunocompromised)
- Famciclovir 250 mg BID, 500 mg BID (for immunocompromised)

Although acyclovir resistance is rare, it does occur in select patients, most specifically those in an immunocompromised state. In these patients, intravenous and intralesional foscarnet or cidofovir have been used with varying success.

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Treatment of Herpes Zoster

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INTRODUCTION

Varicella zoster virus is the causal agent of varicella and herpes zoster (HZ) in humans. HZ results from reactivation of latent varicella zoster virus (VZV) within the sensory ganglia.

Incidence and severity relate with age where >50% of all patients who develop HZ are greater than 60 years old.

A frequent and often very debilitating complication is postherpetic neuralgia, a pain syndrome that develops while or can persist after the dermatomal rash has healed and can be prolonged and greatly affect QOL (quality of life).

There are advantages, but limitations to current therapies for HZ and postherpetic neuralgia.

ETIOLOGY

Herpes zoster is caused by an infection from the varicella zoster virus, which is a member of the family herpesviridae and thus a double-stranded DNA virus with a lipid envelope surrounded by an icosahedral nucleocapsid.¹ The virus is commonly spread by several routes including: direct person-to-person contact, droplet or airborne transmission, respiratory secretions of patients with primary varicella infections, or from the vesicles of patients with herpes zoster. Herpes zoster is a local manifestation of reactivation of latent varicella zoster virus in the dorsal root ganglia or cranial nerve ganglia. Patients with herpes zoster should be considered infectious from the prodromal symptoms begin to 1 week after the appearance of vesiculopustular lesions.²

DIAGNOSIS

Herpes zoster is diagnosed clinically and typically presents as a vesicular rash with an erythematous base in a dermatomal distribution,³ the rash is typically unilateral and accompanied by neuralgic pain. Frequently the neuralgic pain can precede the vesicular lesions by several days. Herpes zoster most commonly affects the thoracic, cervical, and ophthalmic dermatomes. The vesiculopustular

rash typically lasts 7-10 days, and heals within a month. Up to 30% of patients develop complications from herpes zoster, most notably postherpetic neuralgia.²

In 2007, a study was conducted to look at the accuracy of diagnosing acute herpes zoster infections clinically. The study concluded that 91% of cases of clinically diagnosed acute herpes zoster were confirmed on serologic testing in cohort of 260 patients.⁴ Several laboratory tests are available to aide in the diagnosis of herpes zoster; however most are commonly used when the clinical diagnosis of herpes zoster is not obvious.

Other diagnostic testing includes tzanck smears, viral cultures, direct fluorescent antigen assays, and PCR analysis. Tzanck smears are scrapings from the base of the vesicular lesion that characteristically show eosinophilic intranuclear inclusions and multinucleated giant cells.¹ Traditionally this test has a low sensitivity and specificity, failing to differentiate herpes zoster from herpes simplex. Viral cultures provide a definitive diagnosis, but the results usually take 48 hours. Direct fluorescent antigen assays are more sensitive than viral cultures; additionally they have the ability to distinguish between herpes zoster and herpes simplex. PCR analysis is useful in complicated cases and is recommended in patients with suspected varicella virus myelitis, vasculopathy, or zoster sine herpete.³

EPIDEMIOLOGY

Herpes zoster (VZV) HHV-3 has worldwide distribution and 98% of the adult population is seropositive.

HZ is generally considered a disease in patients older than 50 and affects that group more severely, but is also common in younger persons who had primary varicella infection within the first year of life. Individuals with history of primary varicella have a 20% life chance of developing HZ. The severity and incidence of the infection increases significantly with age. The incidences of HZ in the U.S. and Europe are 2.5/1000 between the ages of 20-50, 5.1/1000 between ages of 51-79, and 10.1/1000 in those greater than 80 years of age. The incidence of varicella and

HZ has increased in the immune-compromised population, especially in those affected with HIV.⁵⁻⁶

What are risk factors for HZ especially in RA cohort?

In a national cohort of veterans with rheumatoid arthritis, HZ was 9.96/1000 patient years. Risk factors for HZ included older age, prednisone use, medications used to treat moderate and severe rheumatoid arthritis, malignancy, chronic lung disease, renal failure, and liver disease. Among patients receiving tumor factor α antagonist, etanercept (hazard ratio 0.63) and adalimumab (hazard ratio 0.53) were associated with lower risk of HZ.⁷

What are costs to health system for HZ and PHN?

In the data from the Australian population from 2000 to 2006, zoster and PHN incidence rates were estimated as 10/1000 and 1.45/1000 persons respectively with antiviral prescribed for 73.5% of zoster cases. Total costs to the health system were estimated at 32.8 million a year. The substantial burden of HZ and PHN highlights the benefit of zoster vaccination.⁸

What are effects of varicella vaccine on HZ?

In data from University of Michigan, regarding HZ before and after the introduction of the varicella virus vaccine in the U.S was observed; as the rates of varicella-related hospital discharges and costs have decreased, there has been a significant increase in herpes-zoster-related discharges and changes disproportionately among older adults. HZ vaccine may mitigate these trends for HZ hospitalizations.⁹

The CDC also has addressed speculation that a universal vaccine program might lead to increase in HZ. Incidents have been supported by modeling studies that assume that exposure to varicella boosts immunity and protects against reactivation of VZV as HZ. Such studies predict an increase in HZ incidence until the adult population becomes predominantly composed of individuals with vaccine-induced immunity that does not harbor wild-type VZV. In the United States, a varicella vaccination program was initiated in 1995. Since then, studies monitoring HZ incidence have shown inconsistent findings: two studies have shown no overall incidence, but one study has shown an increase. Studies from Canada and the U.K. have shown increased rates of HZ incidences in the absence of a varicella vaccination program. Data also suggests that unidentified risk factors for HZ are changing over time. Further review of the contribution of these different factors on HZ epidemiology will be challenging.¹⁰

Continued studies are looking at the vaccine and the effects on morbidity of HZ. CDC stated in 2006 a two-dose

varicella vaccine was recommended for the children. Data is inconclusive regarding the effect of the varicella vaccination program on HZ epidemiology.¹¹

The Shingles Prevention Study Group demonstrated that HZ vaccine significantly reduced the morbidity because of HZ and PHN in adults >60 years old.¹²

TREATMENT FOR ADULTS >18 YEARS

Currently there are three US Food and Drug Administration (FDA)-approved medications for the systemic treatment of herpes zoster: acyclovir, valacyclovir, and famciclovir. The intended use of antiviral medications in immunocompetent patients is to accelerate wound healing, minimize the severity of the disease, reduce pain, and reduce the risk and/or duration of post-herpetic neuralgia. The main goal for the use of these medications in immunocompromised patients, in addition to the above, is to halt viral replication and to treat or prevent more severe complications of herpes zoster reactivation, such as ophthalmic herpes zoster (*herpes ophthalmicus*). Bromovinyl deoxyuridine (marketed as brivudin) is another antiviral agent licensed for use in Europe and not in the USA and therefore will not be covered in this discussion.

Immunocompetent Patients

The efficacy of antiviral therapy has been well established by many randomized-controlled clinical trials. These medications are all dependent on viral thymidine kinase (TK). They are phosphorylated to the active form that by viral TK which can then be further phosphorylated to the bi- and triphosphate active forms, which will thus inhibit viral replication. Certain patients should be considered for systemic oral antiviral therapy.¹³ See Table 24-1 for a list of those who would fit the criteria for antiviral administration. Mild cases of zoster with minimal pain involving the trunk in immunocompetent young adults can be managed successfully symptomatically without the intervention of antiviral therapy.

Acyclovir was the first medication approved in the USA for the treatment of herpes zoster. The dosage and recommended use of acyclovir is 800 mg 5 times daily for 7-10 days.¹⁴⁻¹⁵ It has been shown through several randomized, placebo-controlled trials that if treatment is started within 72 hours of lesion onset, at a dose of 800 mg 5 times a day, there is accelerated wound healing and cessation of

TABLE 24-1—Administration Criteria for Antiviral Therapy in Adults (>18y)¹

>= 50 years of age
Moderate to severe pain
Moderate to severe rash
Nontruncal involvement

new lesion formation.¹⁶ It has also been shown through a meta-analysis by Wood et al. that acyclovir was superior to placebo in inducing resolution of moderate to severe zoster-associated pain. The patients experienced pain-free periods starting at 28 days compared to 32 days and were free of pain in 28 days compared to 67 days for acyclovir and placebo, respectively.¹⁷ In a reanalysis of a prior study, Huff et al. showed that acyclovir reduces the pain in patients with chronic zoster, the median time was 20 days versus 62 days with placebo in 187 immunocompetent patients ($P=0.02$).¹⁵

Because of its bioavailability, acyclovir needs to be administered multiple times throughout the day to maintain a therapeutic serum level. Valacyclovir is the pro-drug of acyclovir and has a much better bioavailability, 3-5 times as great. It is metabolized to the active metabolite acyclovir by viral enzymes. When administered as 1g orally 3 times daily, the measured serum levels of valacyclovir are significantly higher. Beutner et al. have shown that acyclovir and valacyclovir share the same time of wound healing when either are initiated within 72 hours of lesion onset, and that valacyclovir is superior to acyclovir in accelerating the resolution of zoster-related pain (median duration of pain, 38 days vs. 51 days; $P=0.001$). They also compared two different dosages of valacyclovir compared to acyclovir in patients greater than 50 years, and confirmed that the proper dosage of valacyclovir should be 1g 3 times daily for 7 days.¹⁸

Famciclovir is dosed at 500 mg 3 times daily for 7 days. Two clinical trials were conducted that compared famciclovir (at several dosages) to either acyclovir or placebo.¹⁹⁻²⁰ In one; a multicenter study was done on 419 immunocompetent adults with uncomplicated herpes zoster. Famciclovir was well tolerated with a safety profile similar to that of placebo. Lesion healing was accelerated and duration of viral shedding was reduced. Patients also experience a two-fold decrease in the duration of post-herpetic neuralgia when compared to placebo recipients. Famciclovir was given in both 500 mg and 750 mg TID for 7 days.²⁰

Tyring et al. compared valacyclovir to famciclovir in a head-to-head randomized-controlled trial. The two proved to be equally effective in accelerating cutaneous wound healing and initiating pain resolution. These two newer antiviral medications are advantageous to the patient over acyclovir because of their ease of administration (being 3 times a day compared to 5 times a day).²¹ See Table 24-2 for dosage schedules for the antiviral medications FDA-approved for herpes zoster.

Three meta-analyses^{17,22-23} and several randomized-controlled trials^{15,18-20,24-26} have demonstrated the effectiveness that antiviral therapy has in reducing the duration and incidence of prolonged pain in patients with herpes zoster.

Orally administered acyclovir, famciclovir, and valacyclovir have been shown to be well tolerated and safe. The most commonly experienced side effects include nausea

TABLE 24-2—Systemic Oral Antiviral Medications for the Treatment of Herpes Zoster in Adults (>18y)

Medication	Recommended Dosage	Duration of treatment, days
Acyclovir	800 mg 5x daily	7
Valacyclovir	1000 mg 3x daily	7
Famciclovir	500 mg 3x daily	7

and headaches (10-20% of patients), but at a rate comparable to placebo.^{18,20,25}

Several studies have also been done to see whether extending the treatment period beyond the recommended 7 days would be beneficial in the treatment of herpes zoster. These studies showed that there may be minimal benefit from the added treatment time, but not significant enough to recommend any further extension of treatment duration. Certain circumstances may lead the clinician to consider extending the treatment beyond 7 days. These may include (but not limited to) persistent vesicle formation, persistent pain, or involvement of the skin, muscles, and eyes that persists beyond the 7 days.^{18,27}

These studies have all shown that when any of the above-mentioned antiviral medications are administered orally within 72 hours of a herpes zoster outbreak, there is a significant reduction in the duration of viral shedding, new lesion formation, and an acceleration of rash healing. They also reduce the duration and severity of the associated pain if administered acutely.

Supplementation with analgesic pain medications is often desired by patients because of their desire to be free of pain. The selection of pain medications may vary on a case by case basis, but the goal should be to maintain a constant level of analgesia rather than a treat as needed situation. See Table 24-3 for a summary of the recommended corticosteroid and analgesic supplementation for the treatment of herpes zoster.

TABLE 24-3—Examples of Oral Corticosteroid and Analgesic Medications Used in the Treatment of Herpes Zoster (>18y)

Medication	Recommended dosage
Oxycodone*	5-30 mg PO q4 hr PRN or 10-160 mg PO q12 hr ER tab (for opioid tolerant patients)
Gabapentin*	300-1200 mg PO TID; Max 3600 mg/day
Prednisone*	60 mg PO daily with slow taper over 21 days

*See entire monograph for each medication for full prescribing information.

Immunocompromised Patients

Patients considered to be immunocompromised are those with disorders of cell-mediated immunity, often because of systemic disease or medical intervention. These patients are at higher risk of developing herpes zoster, and if profoundly immunocompromised can develop disseminated herpes zoster and visceral organ involvement. Those who are at greatest risk of developing herpes zoster are summarized in Table 24-4.

Immunocompromised patients often experience a more dramatic and more serious herpes zoster outbreak, often being more complicated and more common when compared to immunocompetent patients. Initiation of antiviral therapy should begin within 1 week of onset and anytime before full crusting of lesions has occurred. Oral therapy with acyclovir, valacyclovir, or famciclovir can be used in most patients with localized disease and with close clinical observation. Intravenous acyclovir therapy is reserved for those with disseminated disease, those with ophthalmic involvement, severe immunosuppression, and those who are unable to take oral medications. Foscarnet is the drug of choice for the treatment of acyclovir-resistant herpes zoster.²⁸

The recommended dose for intravenous acyclovir in patients with suspected visceral dissemination is 10 mg/kg (or 500 mg/m²) every 8 hours. Once the infection improves and is under control, intravenous therapy can be discontinued and oral therapy initiated.²⁹

For patients who are not as severely immunocompromised, it has been recommended that oral antiviral therapy be initiated with close clinical observation at the same dosages of acyclovir, famciclovir and valacyclovir that are recommended for immunocompetent patients. Famciclovir and valacyclovir may prove more advantageous for this patient population for their bioavailability and ease of administration. It is also recommended that any patient with ocular involvement be evaluated by an ophthalmologist as well as receive intravenous acyclovir, even if it is greater than 72 hours after rash onset.³⁰⁻³¹

Valacyclovir was studied in a randomized, double-blind, controlled trial comparing two dosage regimens and their outcomes in immunocompromised patients: 1g TID versus

2g TID. The results showed no distinct difference in the time to full crusting of the rash, and both dosing schedules were well tolerated, and safe.³² HIV-infected patients have a higher risk of relapsing infection, therefore they should be treated until all lesions have healed, which is often longer than the standard 7-10 day course.¹³ The use of adjunctive corticosteroids in HIV-infected patients has not been studied and thus not recommended until future studies are performed and prove their usefulness.¹³

Atypical presentations or nonresponsive therapies in immunocompromised patients should raise the suspicion of acyclovir-resistant VZV. This resistant virus has a mutation in the gene encoding the viral thymidine kinase, and as a result, the medications used are not activated and therefore are ineffective. Foscarnet or cidofovir may be needed in these patients.¹³

TREATMENT FOR CHILDREN 0-18 YEARS

Primary infection with the VZV virus results in varicella, commonly known as chickenpox. After the primary infection, the virus establishes a latency period in which it will reside in the dorsal sensory ganglia or the cranial nerve ganglia. Reactivation of the virus results in what is commonly known as shingles or zoster. For every 1000 children who present to the pediatrician, one may present with herpes zoster thus making this condition fairly uncommon in children.

Immunocompetent

A prospective cohort study followed 118 immunocompetent pediatric patients with herpes zoster for a period of 6 years to evaluate the long-term sequelae of childhood zoster. After the initial outbreak, patients were evaluated at 1, 3, 6 and 12 months for any residual pain, and again at 3 and 6 years for evaluation of general health. None of the study participants were treated with systemic antiviral therapy. At 3 months, none of the patients reported post-herpetic pain and all continued to be asymptomatic throughout the remainder of the study. From this article, it can be concluded that the likelihood of a healthy pediatric patient developing postherpetic neuralgia is negligible; suggesting that treatment for immunocompetent children with herpes zoster is possibly unnecessary.³³

Feder et al. presented five cases in which immunocompetent children between the ages of 3 and 8 years developed herpes zoster. Based on the presentation and outcome of each patient, the authors concluded that herpes zoster is a rare occurrence in healthy children and is usually a self-limiting condition that does not require treatment. However, ophthalmic involvement of herpes zoster or considerable pain and rash upon presentation are two exceptions in which antiviral therapy of zoster is indicated. Antiviral drugs commonly used against herpes zoster are acyclovir, valacyclovir, and famciclovir.³⁴

TABLE 24-4—At Risk Populations for Developing Herpes Zoster¹

Patients with:	
Lymphoproliferative disorders	
Organ transplant recipients	
AIDS	
Patients receiving:	
Systemic corticosteroid therapy	
Other immunosuppressive medications	

Since all antiviral medications have been shown to be more or less equal in terms of efficacy, the selection of an antiviral agent is often dictated by other factors. For example, acyclovir has relatively poor bioavailability, necessitating frequent dosing and making it less ideal for a patient with poor compliance. Since valacyclovir and famciclovir have excellent absorption and bioavailability, these drugs can be conveniently dosed at less frequent intervals. However, both drugs are only available in oral form, while acyclovir can be administered both orally and intravenously. Thus, a young child or infant who cannot swallow pills is not a candidate for treatment with valacyclovir or famciclovir, and intravenous administration of acyclovir would be preferred in this situation. Cost is also another factor that may influence drug selection; generic acyclovir remains the least expensive treatment among the antiviral medications.³⁵

Immunocompromised

In immunocompromised children, intravenous acyclovir has remained a mainstay of treatment. Small case series have shown effectiveness of oral acyclovir and valacyclovir in immunosuppressed patients; however no official dosing regimen has been established.²⁴

Bomgaars et al. looked at the safety of valacyclovir in immunocompromised children with concurrent herpes zoster infections. Results showed that oral valacyclovir was a safe drug with minimal side effects and authors suggest the use of valacyclovir in the treatment of immunosuppressed pediatric patients with zoster.³⁶

Tyring et al, in a randomized, double-blind, multicenter, acyclovir-controlled study, evaluated the efficacy and safety of famciclovir in immunocompromised patients over the age of 12. Oral famciclovir was dosed at 500 mg 3 times daily, and acyclovir was dosed at 800 mg 5 times daily, each for 10 days following bone marrow solid organ transplantation or chemotherapy. The results of this study revealed that acyclovir and famciclovir were equivocal in terms of pain and length of disease.³⁷

POSTHERPETIC NEURALGIA (PHN)

Post herpetic neuralgia has been defined as persistent pain after an episode of herpes zoster. It is the most frequent complication of herpes zoster. The specific time frame warranting a diagnosis of PHN has been arbitrary ranging from 30-120 days after the resolution of the rash of herpes zoster.³⁸

What are the risk factors for developing PHN?

Older age has long been established as a risk factor for developing PHN. More recent studies have established

additional risk factors including: severe acute pain, severe rash, prodrome preceding the rash. Female sex has been shown to be a risk factor in some studies, but inconsistently reported as a risk factor in others.³⁸

Do corticosteroids have a role in prevention of PHN?

Corticosteroids have historically been advocated in treatment of herpes zoster and prevention of PHN. The adoption of glucocorticoids as being a standard modality for the prevention of PHN was largely based on studies done in the 1950-1980s. These studies were done on small sample sizes (4-40 pts), had inadequate use of controls, and often arbitrary definitions of PHN.⁵⁷⁻⁶⁰

More recent studies, done on larger sample sizes, have demonstrated that corticosteroids do not reduce the incidence of PHN. A randomized double blind, placebo-controlled study evaluated 208 immunocompetent patients 50 years and older. The patients were divided into four groups: acyclovir (800 mg daily 5x/day x 21 days) + prednisone (60 mg/d x 7 days, 30 mg/d x 7 days, 15 mg/d x 7 days); acyclovir + prednisone placebo; prednisone + acyclovir placebo; and acyclovir placebo + prednisone placebo. The group receiving acyclovir + prednisone showed accelerated time to: crusting/healing of the rash, resolution of acute neuritis, return to uninterrupted sleep, return to ADLs, and cessation of analgesic medications. The acyclovir + prednisone group failed to show statistical difference in rates of persistent pain in a 6 month follow-up period. It was concluded that corticosteroids, when used in treatment of herpes zoster, have a role in improving quality of life, but no role in prevention of PHN.³⁹ Another large double blind, controlled trial of 349 patients, confirmed the lack of efficacy of glucocorticoids in the prevention and severity of PHN.⁴⁰ The results of these two studies have been supported by other smaller scale trials.⁶¹⁻⁶⁴

In conclusion, the majority of these studies support the idea that glucocorticoids do not decrease the incidence or severity of PHN. Treatment with glucocorticoids does lead to faster time to rash healing and greater pain reduction during the acute phase of herpes zoster. GC should not be considered standard of care in the treatment of herpes zoster. The risk to benefit ratio must be weighed before using glucocorticoids in the treatment of herpes zoster.

Is gabapentin effective as a first line agent in treatment of PHN?

The mechanism of gabapentin in the treatment of neuropathic pain is unclear, but potentially related to modulation of calcium channels. Chronic neuropathic pain is in part mediated by calcium channels in the spinal cord. Gabapentin modulates these channels. A multicenter, randomized, double-blind, placebo-controlled 8-week

trial showed that gabapentin is effective in treating pain and sleep disturbance associated with PHN. Two hundred and twenty-nine patients were randomized to placebo and gabapentin-treated groups. In the gabapentin group, a 300 mg/d starting dose was initiated. Over a 4 week period, this dose was titrated up to a maximum dose of 3600 mg/d (divided over three doses). The maximum dose was then maintained for another 4 week period. Subjects in the gabapentin group had a statistically significant reduction in daily pain scores from 6.3 to 4.2 points. The placebo group showed only a 6.5 to 6 point reduction. There were no major adverse side effects of gabapentin. Minor side effects included somnolence, dizziness, ataxia, peripheral edema, and infection. Somnolence and dizziness were the most frequently reported side effects, 27.4% and 23.9% respectively. There was no difference in the frequency of side effects reported in the elderly subjects compared with the younger ones. This study concluded that gabapentin should be included as a first line agent for treatment of PHN, because of its statistically significant pain reduction and minor side effect profile.⁴¹

Regarding effective dosing of gabapentin, a large multicenter, randomized, double-blind, 7 week clinical trial compared gabapentin 1,800 mg/day, 2,400 mg/day, and placebo. Doses were tapered up then maintained for 4 weeks. In the gabapentin group, 74/223 reported at least 50% reduction in pain compared to 16/111 in the placebo. No difference in pain reduction was found between the two doses of Gabapentin.⁴²

Pregabalin has also been shown to be effective in the treatment of PHN. In a randomized, placebo-controlled trial, 173 patients were evaluated over 8 weeks. Pregabalin was dosed at 50 mg TID x 3 days, then 100 mg TID x 3 days, and then 200 mg TID for the remainder of the trial. In the group treated with pregabalin, a 30% or more reduction in pain was reported by 63% compared to 25% in placebo ($p=.001$). A 50% or greater pain reduction was reported in 50% of pregabalin subjects versus 20% of placebo ($p=.001$). Overall sleep interference scores were also improved in the pregabalin group ($p=.0001$). Side effect profile was similar to gabapentin, with dizziness and somnolence occurring most frequently.⁴³

Does antiviral treatment prevent post herpetic neuralgia?

A randomized, double blind, multicenter study compared valacyclovir 1,000 mg tid for 7 or 14 days and acyclovir 800 mg 5x/day for 7 days. Total number of patients enrolled was 1,141. The patients were evaluated over a 6 month period. Valacyclovir treatment for 7 and 14 days was shown to have a shorter duration of PHN-associated pain ($p=.001$ and $p=.03$ respectively) when compared to the acyclovir group. The median time to resolution of pain in the valacyclovir 7- and 14-day groups was 38 and 44 days

respectively, compared to 51 days in the acyclovir group. Results showed that valacyclovir demonstrates a 34% faster resolution in pain when compared to acyclovir. The study concluded that valacyclovir accelerates the cessation of PHN-associated pain, decreases the proportion of patients with pain lasting at least 6 months, and had a similar safety profile compared to acyclovir. There was no statistical significance in incidence of PHN between the valacyclovir and acyclovir groups.⁴⁴

Another randomized, double blind, placebo-controlled trial evaluated the effects of famciclovir on PHN. A total of 419 patients were randomized to three groups: famciclovir, 500 mg tid, famciclovir 750 mg tid, or placebo for 7 days. Both famciclovir 500 mg and 750 mg were shown to have more rapid resolution of pain that was statistically significant, when compared to placebo ($p=.02$ and $p=.01$ respectively). There was an approximately 2 month reduction in the duration of PHN. It was concluded that famciclovir was effective in reducing the duration of PHN, but showed no statistical difference in the incidence of PHN.²⁰

Other placebo-controlled, randomized-controlled trials have also been unable to provide convincing evidence that antivirals have a significant effect on the incidence of PHN.⁶⁵⁻⁶⁶

A Cochrane Database Systemic Review investigated the efficacy of antivirals in the prevention of PHN. Five different databases were searched, years ranging from 1966 to 2009. Selection criteria included all randomized and quasi-randomized controlled trials in which antivirals were given within 72 hours of the onset of rash associated with herpes zoster. Six trials with a total of 1211 subjects were evaluated. One trial evaluated famciclovir and the other five acyclovir. Results showed no statistically significant difference in the incidence of PHN occurring in placebo and acyclovir treated patients at 4 months or 6 months after rash onset ($p=.15$ and $p=.62$ respectively). They did show some reduction in the duration of PHN-associated pain. The famciclovir group also did not show decreased incidence of PHN that was statistically significant. The review concluded that acyclovir does not significantly reduce the incidence of PHN and that there are insufficient trials to determine if the other antivirals have a role in prevention of PHN.⁴⁵

Are TCAs or opioids more effective in the treatment of PHN?

Tricyclic antidepressants and opioid analgesics have been widely used as a first line treatment for postherpetic neuralgia.⁴⁶ A double-blind placebo-controlled, crossover trial evaluated opioids, TCA, and placebo in 76 patients with postherpetic neuralgia. The patient population was older than 18 years of age and neuropathic pain had been persistent for at least three months after healing of the rash of herpes zoster. Each patient underwent three different treatment periods, each a total of 8 weeks duration. The three

treatment periods included controlled release morphine sulfate (mean daily maintenance dose 91 mg), nortriptyline (89 mg), and placebo. If the patients could not tolerate either the morphine or nortriptyline, methadone 15 mg and/or desipramine 63 mg were substituted respectively. There was a 1 week wash-out period between each set of treatments. Each study drug was started at low doses and titrated up biw until the patients experienced dose-limiting side effects or maximal relief of their pain.

The study concluded that both opioids and TCAs had statistically significant pain relief when compared to placebo. On a scale of 1-10, mean decrease in pain with TCAs and opioids were 1.4 and 1.9 respectively. Placebo demonstrated only a .2 reduction in pain. The increased pain reduction in the opioids compared to TCAs was not statistically significant ($p=.06$). Despite the higher incidence of side effects including nausea, constipation, drowsiness and dizziness, 53% of the patients preferred opioids over TCAs (30%; $p=.02$). The study concluded that although opioids had more favorable pain control trends when compared to TCAs, it is premature to say that opioids should be first line in place of TCAs in the treatment of PHN. It was suggested that tolerance could be a factor in determining long-term clinical usefulness of opioids in the treatment of PHN. The observation period in this study was only 8 weeks and the authors concluded that further long-term studies are needed to more adequately address the issue of tolerance with chronic treatment.⁴⁷

Is nortriptyline superior to amitriptyline in the treatment of PHN?

Amitriptyline (AT) has been widely used a standard therapy in treatment of PHN. Many trials have shown amitriptyline to have significant effect in pain relief of PHN when compared to placebo.⁶⁷⁻⁶⁸ The downside of treatment with amitriptyline is dose-limiting side effects such as dry eyes, dry mouth, constipation, dizziness, and drowsiness.⁴⁸ Nortriptyline (NT) is a metabolite of amitriptyline that has a much more favorable side effect profile. In a randomized, double-blind, crossover trial of amitriptyline compared to nortriptyline, it was hypothesized that NT may be more effective than AT in treatment of PHN. The study enrolled 33 patients who had moderate to severe pain of more than 3 months (with a median of 13 months) after an outbreak of herpes zoster. A total of 31 patients completed the trial. Each patient was treated by a 5 week course of AT followed by 5 weeks of NT with a 2 week wash-out period in between. Dosing was started at 10 mg for patients >65 years and 20 mg for those <65 years. Doses were titrated up by 10 mg every 3-5 days as tolerated, based on adverse side effects. A steady maintenance dose was achieved for the last 2 weeks of treatment. There was no statistically significant difference in pain reduction between AT and NT. AT was shown to have an increased number of intolerable side

effects when compared to NT ($p=.05$). Dry mouth, constipation, and drowsiness were the most common side effects. The study concluded that NT did not demonstrate statistically significant pain reduction when compared to AT in the treatment of PHN. Based on this study, NT would be superior to AT in regards to its side-effect profile, but not in pain reduction.⁴⁹

What role do topical medications have in the treatment of PHN?

Topical lidocaine and capsaicin have been among the most commonly used and well studied topical treatments for PHN. There have been multiple studies demonstrating efficacy of capsaicin cream (025%-075%) in the treatment of PHN.⁶⁹⁻⁷⁰ The cream must be applied multiple times per day for weeks at a time to achieve significant pain relief. Adverse effects such as burning, stinging, and erythema at application site can be unbearable in many patients limiting their use.⁶⁹⁻⁷⁰ A recent randomized, double-blind study evaluated the efficacy of a one-time application of high concentration capsaicin patch (8%), called NGX-4010. The goal of the study was to evaluate efficacy, tolerability and safety of high concentration capsaicin as a treatment for PHN. Four hundred and two patients, experiencing post herpetic pain for at least 6 months, were randomized to either the NGX-4010 group (8% capsaicin), or the control group receiving low-dose capsaicin patch (.04%). The capsaicin patches were applied once for 60 minutes duration. The patients were followed for an 8-12 week period, after the single patch application, to evaluate pain response. Change in the NPRS score (0-10 scale of pain scoring) from baseline was evaluated. Patients in the NGX-4010 group had statistically greater decrease in pain, at weeks 2 and 8, when compared to the control group. For the NGX-4010 group, the mean change in NPRS score was 29.6% compared to 19.9% in the placebo group ($p=.001$). Side effects in the NGX-4010 group such as erythema and pain at application site were common, but mild and self limited. The study concluded that one 60-minute application of high concentration 8% capsaicin patch, NGX-4010, can significantly reduce the pain of PHN for up to 12 weeks after the single application. Side effects are mild and self limited at the site of application. There are no adverse systemic side effects related to treatment with the patch.⁵⁰

Topical lidocaine 5% patch was approved by the FDA in 1999 as the first medically indicated treatment for PHN. There have been many studies reporting its efficacy in PHN-associated pain reduction.⁷¹⁻⁷² A randomized, double-blind, vehicle controlled study evaluated efficacy of lidocaine 5% patch in reduction of neuropathic pain. Ninety-six patients reported to have moderate to severe PHN-associated pain were evaluated. Pain was evaluated using the neuropathic pain scale (NPS) which includes ten different pain descriptors. Pain was evaluated at baseline

then re-evaluated after daily lidocaine 5% patch use for 3 weeks. Those in the lidocaine patch group were shown to have a decrease in NPS from baseline of 51.7 to a score of 36.4 at 3 weeks. Those in the vehicle group had an initial NPS score of 53.8 dropping to 46.1 at 3 weeks. Lidocaine patch was shown to have a statistically significant overall pain reduction when compared to the vehicle ($p=.043$).⁵¹

Is there a future for botox in the treatment of PHN?

Botulinum A toxin has been used in the treatment of many neurologic diseases including tics, migraines, and cervical dystonia. There have recently been many case reports documenting its efficacy in treatment of neuropathic pain, but is not yet a well studied treatment option and therefore not a standard of care.⁷³⁻⁷⁴ One case reported efficacy of botox in an 80-year-old male with PHN. The patient had been treated with TCAs, gabapentin, and carbamazepine without improvement of his pain. Pain reduction was finally achieved with increased doses of TCAs, gabapentin, and addition of morphine. The patient subsequently developed severe delirium and had to stop all oral medications. The patient was then treated with a thoracic epidural of 1 ug/mL of fentanyl in .25% bupivacaine infused at 5 mL/hr. The patient still experienced severe and persistent pain. A trial of BTX-A was used for the recalcitrant PHN associated pain. A total of 100 units of BTX-A were injected in a fanning pattern in the subcutaneous plane. A 23-gauge needle was used at four different sites in the area of pain. At each of the four sites, 20 routes of injection were done in a fanning pattern. Five units of BTX-A per route were injected at each of the four sites. Two days after the injection, pain was reduced from a 10 down to a 1 on the VAS (visual analog score). The pain relief lasted for a total of 52 days. The pain returned after this 52-day period.⁵²

In conclusion, BTX-A may be an emerging therapeutic option in treatment of PHN, but controlled studies will be necessary to further evaluate BTX-A in treatment of PHN.

ZOSTER VACCINE LIVE (ZOSTAVAX)

In 2006, US Food and Drug Administration approved Zoster Vaccine Alive (Zostavax) for the prevention of HZ in immunocompetent adults age 60 and over. The approval was based on the results of multicenter clinical trial, the Shingles Prevention Study. This study showed the vaccine significantly decreased incidence of shingles, burden of illness because of disease, and the development of as well as severity of, postherpetic neuralgia.⁵³

In a randomized, double blind, placebo-controlled trial with 38,546 patients greater than 60 years of age, the vaccine decreased number of illness because of HZ by 61.1% ($p < .001$), decreased the incidence of postherpetic

neuralgia by 66.5% ($p < .001$) and decreased incidence of HZ by 51.3% ($p < .001$).⁵⁴

The study had 95% of subjects continued to completion, with a median of 3.12 years of surveillance for HZ. A total of 957 cases of HZ (315 among vaccine recipients and 642 among placebo recipients) and 107 cases of PHN (27 among vaccine recipients and 80 among placebo recipients) were included in the efficacy analysis. The conclusion was the zoster vaccine markedly reduced morbidity from HZ and PHN among older adults.⁵⁵

RISK OF HZ IN PATIENTS ON ANTI-TNF ALPHA AGENTS (ANTI-TNF A)

These new agents are approved for rheumatoid arthritis, JIA (juvenile idiopathic arthritis), psoriatic arthritis, ankylosing spondylitis, and Crohn's CUC and little is known about the reactivation of latent viral infections.

Are Patients undergoing treatment with anti-TNF α agents at increase risk for developing herpes zoster?

Patients undergoing treatment with anti-TNF α inhibitors have been well known to be at increased risk for bacterial and opportunistic infections. Not much is known about the risk of viral infections or reactivation of latent viral infections associated with anti-TNF therapy. A recent prospective cohort investigated this idea in a population of RA patients undergoing treatment either DMARDs or one of the anti-TNF α inhibitors, including the anti-TNF α antibodies (adalimumab, infliximab) and etanercept. A total of 5040 patients were followed prospectively from 2001 to 2006. There were 86 cases of zoster reported in 82 patients. Thirty-nine of the cases were in those treated with anti-TNF α monoclonal antibodies (adalimumab and infliximab), 23 in etanercept and 24 in those treated with DMARDs. For the monoclonal antibodies, the crude incidence rate per 1000 patient-years was 11.1 (95% confidence interval, 7.9-15.1), for etanercept 8.9 (95% CI, 5.6-13.3), and for the DMARDs 5.6 (95% CI, 3.6-8.3). After adjusting for variables such as RA severity, age, and glucocorticoid use, there was an increased risk of herpes zoster in the anti-TNF α anti-body group (HR, 1.82 [95% CI, 1.05-3.15]). However, this increased risk was not high enough to be clinically significant. There was no significant increase in the etanercept group (HR, 1.63 [95% CI, 0.73-2.55]) or for anti-TNF α therapy when considered as a class (HR, 1.63 [95% CI, 0.97-2.74]). This study concluded that there may be an increase risk of herpes zoster in patients treated with anti-TNF α antibodies such as adalimumab or infliximab, but the anti-TNF α drugs as a whole do not demonstrate statistically significant increased risk of herpes zoster.⁵⁶ There have been other RCTs that have documented an increase incidence of herpes zoster in patients treated with

What We Know

- Varicella zoster virus is the causal agent of varicella and herpes zoster in humans. HZ results from reactivation of latent varicella zoster virus within the sensory ganglia. It has worldwide distribution and greater than 98% of adult population is seropositive. A frequent and often very debilitating complication is PNH, a pain syndrome that develops while on, or can present after the dermatomal rash has healed and can be prolonged and greatly affect the quality of life.
- The zoster vaccine live (Zostavax) markedly reduces morbidity from HZ and PHN among adults greater than 60 years of age.
- Glucocorticoids do not decrease the incidence or severity of PHN. Acyclovir does not significantly reduce the incidence of PHN. Nortriptyline is superior to amitriptyline in regards to its side effect profile, but it does not show increased pain reduction in the treatment of post-herpetic neuralgia.

infliximab or adalimumab⁷⁵), but further RCT must be done to further evaluate the clinical significance of these findings.

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Treatment of Impetigo

25

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INTRODUCTION

Impetigo contagiosum, spread by skin-to-skin contact, as well as through fomites, represents a superficial cutaneous bacterial infection. *Staphylococcus aureus* and much less commonly *Streptococcus pyogenes* cause impetigo.

EPIDEMIOLOGY

Impetigo commonly affects children and athletes with intense skin-to-skin contact or extensive exposure to colonized environments or fomites. Recent studies document the routine presence of *Staphylococcus aureus* on the surfaces of sports-related areas.^{1,2} For instance, in one study, investigators sampled for the presence of methicillin-resistant *Staphylococcus aureus* (MRSA) at nine Ohio high school wrestling and healthcare facilities.² All sites had MRSA; and nearly 90% of the tested surfaces of inner and outer circles of the wrestling mats demonstrated MRSA. Locker room benches (78%) also frequently possessed MRSA. Just over 50% of sampled treatment tables and locker room sinks had MRSA. Even the athletic training room doorknob demonstrated MRSA in 20% of the swabs.

A similar study, in the same area of the country, examining the environment of the athlete, discovered that 90% of athletic facilities possessed two or more positive MRSA surfaces.¹ In this study, the water coolers possessed the highest occurrence of MRSA (80%). Like the other study, locker room sinks and treatment tables demonstrated MRSA in 50-70% of the samples. These studies illustrate the prevalence of MRSA in the athletic environment and may explain, in part, the epidemics of impetigo observed in athletes.

ETIOLOGY AND DIAGNOSIS

Both methicillin resistant and methicillin sensitive variants of *Staphylococcus aureus* exist. This chapter extensively reviews the treatment of impetigo contagiosum and will only briefly discuss diagnostic aspects. Impetigo may occur as a primary infection, by affecting otherwise healthy skin, but also may complicate previously diseased skin. Dermatitis, such as atopic dermatitis and venous stasis dermatitis can commonly develop secondary impetiginization as these gram-positive organisms infect the perturbed epidermis.

Impetigo, in its mature presentation, appears as well defined, erythematous, and often honey-colored crusted, scaling papules and plaques. In athletes, these lesions especially occur in areas of skin-to-skin contact. The differential diagnosis of typical mature impetigo includes crusted and exudative dermatitis, lupus erythematosus, tinea corporis, and crusted herpes virus infection. The lack of characteristic findings of honey colored crust, in the early stages of disease, makes the diagnosis challenging. For instance, for reasons related to disqualification from competition, athletes present to the clinician soon after the development of nonspecific erythematous papules. Based solely on the clinical morphology of these very early lesions, the clinician will find it extremely difficult to distinguish acne, dermatitis, lupus erythematosus, and other infections such as tinea corporis and herpes simplex virus infection. As the lesions age, they acquire morphologic features that help the clinician differentiate among these cutaneous disorders.

Rarely, a bullous variety of impetigo occurs; the differential diagnosis of this variant includes bullous arthropod reaction and immunobullous disorders.

THERAPEUTIC APPROACH

Studies have not investigated the usefulness or optimal frequency and duration of nonpharmacologic approaches to impetigo. However, infected individuals should apply warm and moist compresses to the affected area several times per day for five to 10 minutes each time. Furthermore, individuals who develop impetigo should cover the area to prevent the spread to other individuals.

The main pharmacologic treatments for impetigo include topical and oral antibiotics. Many studies have studied the effectiveness of each against placebo and even against each other. A lack of information exists wherein studies compare a combination of topical and oral agents versus a single route of administration.

In the past decade, two large meta-analyses examined the treatment of impetigo. George and Rubin published a systematic review of the treatments for impetigo in 2003.³ Three hundred and fifty-nine studies fulfilled their criteria. They narrowed their search to include double-blind or observer-blind randomized control trials and to exclude non-English studies and those studies lacking in other specific data. Additionally, the authors also

wrote to pharmaceutical companies but did not detect any other relevant studies. Ultimately, only 16 studies from 1966–2002 satisfied their criteria for inclusion in their meta-analysis. The methodologies of these sixteen studies varied on several elements including subject age, comparative medications, duration of treatment, and time of assessment.

Seven studies treated infected individuals for 7 days,^{4–10} four studies treated infected subjects for 10 days,^{11–14} and three reports treated subjects for 14 days.^{15–17} One study treated subjects until clearance¹⁸ and one study only treated patients for 6 days.¹⁹

The four broad comparative groups among these studies included oral therapies compared to each other, topical antibiotics versus placebo, topical antibiotics against each other, and topical antibiotics compared to oral antibiotics. This meta-analysis only included two studies comparing only oral antibiotics in the treatment of impetigo. Demidovich et al.¹³ compared penicillin V, cephalexin, and erythromycin, while Jaffe et al.¹¹ compared amoxicillin and clavulanic acid with cefaclor. Three studies studied topical antibiotics versus placebo. Eells et al.⁵ Koning et al. 2002,¹⁷ and Zaynoun 1974⁴ studied topical 2% mupirocin, 2% fusidic acid cream, or gentamycin versus placebo, respectively.

Also in this meta-analysis, seven included studies evaluated head-to-head topical antibiotics; 2% mupirocin ointment versus 2% fusidic acid represented the most common comparison.^{6–8,10,15,16,18} The last comparative group investigated various oral antibiotics against various topical antibiotics. These investigators compared oral erythromycin (taken three to four times daily) or cephalexin to topical bacitracin or 2% mupirocin.^{9,12,14,19}

Overall, in this particular meta-analysis, topical antibiotics demonstrated a greater response in impetigo than placebo with an odds ratio of 2.69 and a 95% confidence interval of 1.49–4.86.³ No differences existed between topical 2% mupirocin ointment and 2% fusidic acid with an odds ratio of 1.76 and a confidence interval that included one [95% CI = 0.77–4.03]. While the pooled data

comparison between oral erythromycin and topical 2% mupirocin ointment or bacitracin revealed an odds ratio of 0.48, suggesting that topical antibiotics represented a superior therapy, the confidence interval included one [95% CI = 0.23–1.00]. The authors of this meta-analysis did not calculate a pooled odds-ratio for the two studies comparing oral antibiotics.³

This meta-analysis appropriately identified important limitations of their work. The outcome measures, specifically cure, varied among the studies. The duration also varied among the studies, though the authors suggest 7 days represents effective treatment duration. Last, most of the studies included in this meta-analysis involved very small numbers. The largest study of impetigo treatment involved 201 subjects; the median number of subjects in the 16 trials was only 60.

In summary, very few high-quality studies exist that critically compare topical antibiotics to other topical antibiotics or oral antibiotics. George and Rubin's meta-analysis nevertheless revealed that topical antibiotics clear impetigo significantly better than placebo and at least as well as oral erythromycin (Table 25-1).³

A larger meta-analysis searched several electronic databases as well as hand searched several references dating back to 1938.²⁰ The authors placed no restrictions on study language and they contacted pharmaceutical companies for data on unpublished or ongoing studies. The investigators included both bullous and nonbullous impetigo in their analysis. The authors identified fifty-seven trials that met their inclusion criteria that amounted to an overall total of 3533 subjects.

Interestingly the only study included in this systematic review, which compared oral antibiotics to placebo, found no statistical difference in the effect between oral penicillin and placebo in the treatment of impetigo.²¹ The pooled analyses of all studies comparing cephalosporins to other oral antibiotics revealed no statistical differences (odds-ratio = 1.67, 95% CI=0.93–3.00), while no cephalosporin performed better than another cephalosporin antibiotic in the treatment of impetigo (odds-ratio = 0.56,

TABLE 25-1—Summary of the Current Evidence for Impetigo

	Bacitracin	Mupirocin	Fusidic Acid	Rapamulin	Oral Antibiotics
Bacitracin					
Mupirocin	Mupirocin ++				
Fusidic Acid	Equivocal	Equivocal			
Rapamulin	No studies	No studies	Equivocal		
Oral Antibiotics	Unclear	Mupirocin ++	Fusidic Acid ++	No studies	
Placebo	Bacitracin +	Mupirocin +++	Fusidic Acid +++	Rapamulin +++	Unclear

+, weak evidence in favor of the medication

++, moderate evidence in favor of the medication

+++, strong evidence in favor of the medication

95% CI=0.24-1.31).²⁰ Furthermore, in their meta-analysis, no oral macrolides performed better than penicillin and its variants (odds-ratio = 1.99, 95% CI=0.92-4.34).²⁰ In summary, pooled analysis cast doubt on the superiority of any one oral antibiotic for treating impetigo.

Five studies examined topical antibiotics versus placebo in nonbullous impetigo; three additional reports, not included by George and Rubin³, studied specifically 2% mupirocin^{22,23} or bacitracin versus placebo.²¹ Unlike George and Rubin³, Koning et al.²⁰ did not include topical gentamycin compared to placebo in the analysis. Overall analysis revealed that topical antibiotics led to better improvement and cure rates than placebo with an odds-ratio of 6.49 (95% CI= 3.93-10.73).²⁰ Bacitracin failed to demonstrate superiority over placebo in one trial, although this study had limited enrollment and a large confidence interval.²¹

The authors included twelve studies examining the effect of topical antibiotics against each other. None of the individual studies demonstrated the success of one topical antibiotic over another. The overall analysis demonstrated an odds-ratio of 1.56 (95% CI= 1.09-2.24).²⁰ Many of the studies that did not show a significant difference between topical antibiotics had very small numbers eliciting a potential question of inadequate power to detect a difference.

The largest group of studies analyzed in this review involved topical antibiotics compared to oral antibiotics. Ten studies, comparing 2% mupirocin with erythromycin noted significantly better cure or improvement with 2% mupirocin (odds-ratio 1.76, 95% CI =1.05-2.97).²⁰ The authors also sub-pooled the three highest quality studies^{9,12,24} of these 10 reports and documented an odds-ratio of 3.73 (95% CI=1.35-10.34) strongly in favor of 2% mupirocin.²⁰ Other trials examined 2% mupirocin versus dicloxacillin,²⁵ cephalexin¹⁴, and ampicillin²⁶ and discovered no statistical difference between the groups. When the investigators included all studies that met their criteria, topical antibiotics (including bacitracin, fusidic acid, and 2% mupirocin), in general, possessed a slightly greater effect on impetigo than oral antibiotics with an odds-ratio of 1.6 (95% CI =1.12-2.29).²⁰ Many of the nonmupirocin topical antibiotics versus oral antibiotics studies yielded mixed results. For instance, no differences existed between bacitracin and erythromycin¹⁹ or penicillin,²¹ while oral cephalexin performed superiorly to bacitracin in another trial.¹⁴

Two studies examined the differences in effect between topical antibiotics and disinfecting treatments. One study found that hexachlorophene cleared impetigo no better than bacitracin (odds-ratio 3.97, 95% CI=0.15-104.18).²¹ Furthermore, another found no statistical difference between 2% fusidic acid and hydrogen peroxide;²⁷ however, a weighted summary of both studies discovered that topical antibiotics performed superiorly compared to hexachlorophene or hydrogen peroxide.²⁰

In summary, the extensive systematic review performed by Koning et al.²⁰ fails to identify a superior oral antibiotic for the treatment of impetigo. In addition, several well-designed studies note a significantly better clearance with 2% mupirocin over oral antibiotics. Mixed results exist regarding topical bacitracin as it performed as well compared to oral antibiotics in one study, and less well in another study. Likewise, topical bacitracin cleared impetigo as well as placebo in other contradictory trials (see Table 25-1).

Importantly, these two main meta-analyses did not include the first new topical antibiotic developed in many years. A recent novel FDA-approved topical antibiotic, 1% retapamulin, represents the first pleuromutilin antibacterial agent for the treatment of superficial skin infections. Two major studies have compared the effectiveness of 1% retapamulin to other topical agents in impetigo. No studies exist that compare 2% mupirocin and 1% retapamulin. Furthermore, in primary impetigo, no studies have compared the response rates of 1% retapamulin with that of oral antibiotics.

In a randomized, double-blind trial, topical 1% retapamulin achieved clinical success significantly more often than placebo and cleared both *Staphylococcus aureus* and *Streptococcus pyogenes*.²⁸ In this particular study, researchers compared 5 days of twice daily use of both agents. The investigators randomized 213 patients in a 2:1 ratio; 139 subjects applied 1% retapamulin and 71 subjects applied placebo. Eighty-six percent of the subjects treated with 1% retapamulin cleared, whereas 52% of those subjects treated with placebo cleared ($p<.0001$). The most common side effects in either treatment group were pruritus, paresthesias, and irritation.

Other investigators conducted a noninferiority study comparing 1% retapamulin to 2% sodium fusidate ointment.²⁹ This randomized, observer-blinded study found that in the intention-to-treat analysis, 1% retapamulin ointment applied twice daily for five daily had a ninety-five percent response rate, whereas 2% sodium fusidate ointment used three times daily for seven days demonstrated a 90% percent response rate. One percent retapamulin did not demonstrate superiority over 2% sodium fusidate ointment (see Table 25-1).

CONCLUSIONS

Despite the common occurrence of impetigo, few studies carefully examine the various treatment options. Meta-analysis, however, has shown that topical 2% mupirocin ointment clears impetigo at least as well as oral antibiotics. The topical application of this antibiotic also avoids the several potential side effects associated with systemic medications. The novel agent, topical 1% retapamulin, performs better than placebo; future studies need to compare this medication to topical 2% mupirocin and oral antibiotics. Furthermore, future work should also investigate the combination of topical and oral antibiotics compared to each individually.

What We Know

- Topical 2% mupirocin and 2% fusidic acid clear impetigo greater than placebo.
- No differences exist in effects between 2% mupirocin and fusidic acid.
- Topical antibiotics (2% fusidic acid or 2% mupirocin and perhaps bacitracin) clear impetigo as well as oral antibiotics and while not statistically significant, topical 2% fusidic acid and 2% mupirocin may perform better than oral agents.
- Topical 1% retapamulin performs greater than placebo, although 1% retapamulin demonstrates noninferiority to that of fusidic acid.

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Treatment of Tinea Capitis

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INTRODUCTION

Tinea capitis is a dermatophytic infection of the scalp and hair. It is seen primarily in pre-adolescent children.

EPIDEMIOLOGY AND ETIOLOGY

Tinea capitis may be caused by any pathogenic dermatophyte from the genera *Trichophyton* and *Microsporum* except *T. concentricum*.¹ It has a worldwide distribution and the predominant species of dermatophyte responsible varies between different regions. In the United States, more than 95% of tinea capitis are caused by *T. tonsurans*.² In Europe, the most common pathogen is *T. tonsurans* in the United Kingdom, *Microsporum canis* in Central and Southern Europe, and *T. violaceum* in Greece and Belgium.³ *Microsporum canis* is a common organism in the developed countries worldwide and this has been attributed to tourism to endemic regions (such as the Mediterranean countries) and the close proximity between humans and companion animals.⁴ Several dermatophyte species, on the other hand, are geographically limited. *T. soudanense* is a common and endemic cause of tinea capitis in northwestern tropical Africa and West Asia.⁴

CLINICAL MANIFESTATION

Tinea capitis often presents with scaly patches on the scalp and a variable degree of inflammation. Clinical patterns include ectothrix, endothrix, favus, and kerion. Asymptomatic carriers have been found in families of up to 50% of children with tinea capitis.^{5,6}

Ectothrix

This presents as multiple circular patches of alopecia with broken-off hairs and scaling. The dermatophyte grows on the external surface of the hair, destroying the hair cuticle. Mycelium can be visualized on the external surface of the hair shaft under direct microscopy with potassium hydroxide preparation. Certain species fluorescence under Wood's light and this is because of the production of pteridine. These species include *Microsporum canis*, *M. audouinii*, *M. ferrugineum*, *M. distortum*, *M. gypseum* (sometimes), and *T. schoenleinii*. Ectothrix dermatophytes which do

not fluorescent under Wood's light include *Trichophyton rubrum*, *T. mentagrophytes*, *T. verrucosum*, *T. megninii*, *M. gypseum*, *M. nanum*. Therefore, if the infected hair of patient fluorescence under Wood's light, the infecting dermatophyte likely belongs to the *Microsporum* species.

Endothrix

The dermatophyte infects the interior of the hair shaft and under microscopy with potassium hydroxide preparation, mycelium can be seen within the hair shaft. The cuticle of the hair shaft is intact. This pattern is sometimes known as 'black dot ringworm' because remnants of broken brittle hair appear as black dots on the surface of the scalp. The infecting species include *T. rubrum*, *T. tonsurans*, *T. violaceum*, *T. soudanense*, *T. gourvillii*, and *T. yaoundei*.

Favus

This is a chronic inflammatory form of tinea capitis, which can lead to scarring alopecia. It is characterized by yellowish cup-shaped crusts (known as scutula) surrounding infected hair follicles. These crusts consist of hyphae and keratinous debris. It is primarily due to *T. schoenleinii* infection and is occasionally due to *T. violaceum* and *M. gypseum*. Hyphae and airspaces are seen within the hair shaft under direct microscopy with potassium hydroxide preparation.

Kerion

A severe acute inflammatory reaction to dermatophytic elements may result in a painful boggy mass associated with formation of pustules and regional lymphadenopathy. This may result in scarring alopecia. The most frequent pathogens are *M. canis*, *T. mentagrophytes*, *T. tonsurans*, and *T. verrucosum*.

DIAGNOSIS

The diagnosis of tinea capitis can be confirmed by microscopic examination (with potassium hydroxide preparation) and/or culture of plucked infected hair, skin scrapings, or skin swabs. Specimens for culture can be obtained with

the cotton swab technique, using the sterile swab stick transport medium set that one normally uses to perform a bacterial swab culture.⁷ The swab stick is moistened with tap water, and suspicious areas of the scalp are vigorously swabbed. The swab stick is then replaced into its container and sent to the lab for mycologic culture.

Microscopic examination with 10 to 20% potassium hydroxide preparation can provide a rapid diagnosis of tinea capitis but accurate evaluation is difficult in inexperienced hands. Culture is a better method of diagnosis for most practitioners, is more sensitive than microscopy but results may take 4 to 6 weeks. There was a recent publication on a new polymerase chain reaction-based restriction fragment length polymorphism (PCR-RFLP) method, which targets the 18S ribosomal DNA and internal transcribed spacer (ITS) region of fungi, and this allows for rapid detection and identification of dermatophyte species within 24 hours.⁸

TREATMENT

The primary aim of treatment is to achieve complete cure, clinically, and mycologically, using an agent with minimal side effects. As tinea capitis mainly affects children, besides efficacy and safety, the ease of administering the course of antifungal drug is important. A preparation with a more pleasant taste requiring a shorter duration of treatment will enhance the compliance rate of the therapy in children.

Griseofulvin is the systemic antifungal agent with the longest clinical track record. It has proven to be safe, is relatively inexpensive, comes in both tablet and suspension preparations, and is widely available. However, it has a bitter taste, has to be taken with meals, and needs to be taken for a rather long duration (usually 8 weeks).

Newer antifungal agents, such as terbinafine, itraconazole, and fluconazole, are increasingly being used because of their shorter duration of treatment, more consistent absorption rates, and longer periods of retention in infected tissues. They have also been shown to be safe in previous meta-analyses.^{9,10}

COMPARISON OF NEWER ANTI-FUNGAL AGENTS IN EFFICACY AND SAFETY TO GRISEOFULVIN IN THE TREATMENT OF TINEA CAPITIS

Methods

Inclusion Criteria and Outcome

Only randomized controlled trials (RCTs) comparing different systemic antifungal drugs for the treatment of tinea capitis were included. The subjects were children and adults with normal immunity with the diagnosis of tinea capitis confirmed by the presence of dermatophytes under microscopy and/or culture.

The primary outcome measure was the complete cure rate. Complete cure was defined as achieving both clinical and mycologic cure. The secondary outcome measures were:

- Mycologic cure rate (mycologic cure referred to negative results on microscopy and culture).
- Clinical cure rate (clinical cure referred to the resolution of clinical symptoms and signs)
- Severity and frequency of adverse effects.

Search methodology

A search of the MEDLINE, EMBASE, Cochrane Central Register of Clinical Trials, and the Cochrane Skin Group Ongoing Skin Trials Register was performed in October 2009 using the terms 'tinea capitis', 'griseofulvin', 'terbinafine', 'itraconazole', 'fluconazole', and 'ketoconazole'.

Data Collection

The titles and abstracts of all retrieved articles were screened with the inclusion criteria by two reviewers (Tey and Chan). For abstracts in which the study design was unclear, the full texts were reviewed. Subsequently, the full texts of all the articles selected were reviewed and data was extracted using a predesigned form.

Data Analysis

All analyses were performed using STATA Release 10 (STATA Corp, College Station, Texas). Pooling of treatment effect was accomplished using a random-effects model (DerSimonian and Laird method¹¹). Odds ratio (OR) were calculated such that values less than 1 favors griseofulvin and values more than 1 favors terbinafine. The I² test is used to check for heterogeneity of effect measures among the studies.

A study that included only *Microsporum* species found that the cure rate of griseofulvin tended to be higher than terbinafine.¹² Another study found that terbinafine was significantly better than griseofulvin in mycologic, clinical, and complete cure rates among patients with *T. tonsurans* infection. The study also found that griseofulvin was significantly better than terbinafine in mycologic and clinical cure rates among patients with *M. canis* infection.¹³ A subgroup analysis based on different dermatophyte species (*Microsporum* and *Trichophyton*), was therefore performed in this review. Adverse effects are described qualitatively.

Results

Included Studies

Seventeen trials involving 3635 subjects comparing different systemic antifungal treatments for tinea capitis were identified (Table 26-1). They were conducted between 1985 and 2008.

TABLE 26-1—RCTs Comparing Different Systemic Anti-Fungal Treatments for Tinea Capitis

Study	Year	Location	N	Comparative drugs		Outcome	Assessment (wk)
Caceres-Rios ¹⁴	2000	Peru (Lima)	50	Griseofulvin	Terbinafine	Complete cure	12
Dastghaib ¹⁵	2005	Iran	40	Griseofulvin	Fluconazole	Complete cure	8
Elewski ¹³	2008	Multiple centers around the world	1549	Griseofulvin	Terbinafine (oral granules)	Complete cure	10
Foster ¹⁶	2005	USA, Guatemala, Chile, Costa Rica, India	880	Griseofulvin	Fluconazole	Complete cure	10
Fuller ¹⁷	2001	UK	210	Griseofulvin	Terbinafine	Complete cure	24
Gan ¹⁸	1987	USA (Dallas)	80	Griseofulvin	Ketoconazole	Complete cure	8
Gupta ¹⁹	2001	Canada & South Africa	200	Griseofulvin	Terbinafine Itraconazole Fluconazole	Complete cure	12
Haroon ²⁰	1995	Pakistan	105	Griseofulvin	Terbinafine	Complete cure	12
Jahangir ²¹	1998	Pakistan	55	Terbinafine	Itraconazole	Complete cure	12
Lipozencic ¹²	2002	Europe and South America (22 centers)	165	Griseofulvin	Terbinafine (of different durations)	Complete cure	16
Lopez-Gomez ²²	1994	Spain (Madrid)	35	Griseofulvin	Itraconazole	Complete cure	12
Martinez-Roig ²³	1988	Spain (Barcelona)	13	Griseofulvin	Ketoconazole	Clinical cure	6
Memisoglu ²⁴	1999	Turkey	78	Griseofulvin	Terbinafine	Complete cure	12
Rademaker ²⁵	1998	New Zealand	24	Griseofulvin	Terbinafine	Clinical cure	12
Tanz ²⁶	1985	USA (Chicago)	22	Griseofulvin	Ketoconazole	Mycological cure	12
Tanz ²⁷	1988	USA (Chicago)	79	Griseofulvin	Ketoconazole	Complete cure	12
Wahab ²⁸	2007	Bangladesh	50	Griseofulvin	Fluconazole	Clinical and mycological cure	8

All the trials compared efficacy between different drugs. There were no trials comparing active treatment to placebo. Griseofulvin has been used as the standard for comparison in all studies, except for one which compared terbinafine to itraconazole.²¹ Griseofulvin was compared with terbinafine in eight studies (seven used terbinafine tablets and one used oral granules), with itraconazole in three studies, with fluconazole in four studies, and with ketoconazole in four studies.

The studies included subjects from most parts of the world. The assessment period was usually 12 weeks but ranged from 6 to 24 weeks. All studies reported complete cure except for four, of which two reported clinical cure as the outcome^{23,25}, one reported mycologic cure²⁶, and one reported both clinical and mycologic cure²⁸. All but one study¹⁸ reported adverse events.

Griseofulvin

Comparative Efficacy

Griseofulvin has been considered the gold standard for treatment of tinea capitis and it has been used to compare against newer antifungal agents.

With regard to *Trichophyton* species, a study involving 200 participants demonstrated no significant difference in

efficacy between 6 weeks of griseofulvin and 2 to 3 weeks of itraconazole, terbinafine, and fluconazole, although griseofulvin tended to be more effective.¹⁹

There is only one RCT in which *Microsporum* species accounted for the majority of the pathogens.¹² In this study, *M. canis* constitutes 98.5% of the *Microsporum* species. This study was not powered adequately for a statistical comparison between terbinafine and griseofulvin, but the cure rates tended to be lower in the terbinafine groups than in the griseofulvin group.

Adverse Effects

Griseofulvin was associated with a small number of adverse effects in the studies reviewed. These include gastrointestinal symptoms (vomiting, abdominal pain, diarrhea), headache, upper respiratory tract symptoms (nasopharyngitis, cough, infection), and rashes. No severe adverse effects have been noted.

Terbinafine

Comparative Efficacy

Seven studies comparing griseofulvin and terbinafine in 2163 subjects were analyzed and their characteristics are

TABLE 26-2—Characteristic of Studies Comparing Griseofulvin and Terbinafine

Study	Year	Location	N	Age	% of <i>Trichophyton</i> species	% of <i>Microsporum</i> species	Griseofulvin dosing	Griseofulvin duration (wks)	Terbinafine dosing	Terbinafine duration (wks)
Haroon ²⁰	1995	Pakistan	105	2 to 65	99%	1%	Gc	8	Ta	4
Memisoglu ²⁴	1999	Turkey	78	2 to 13	49%	48%	Gc	8	Ta	4
Caceres-Rios ¹⁴	2000	Peru (Lima)	50	1 to 14	74%	26%	Gc	8	Ta	4
Fuller ¹⁷	2001	UK	147	2 to 16	84%	14%	Gb	8	Ta	4
Gupta ¹⁹	2001	Canada & South Africa	100	5.8 (mean)	100%	0%	Ga	6	Ta	2 to 3
Lipozencic ¹²	2002	Europe and South America (22 centers)	134	7.7 (mean)	0%	100%	Ga	12	Ta	6 to 12
Elewski ¹³	2008	Multiple centers around the world	1549	4 to 12	65%	34%	Gd	6	Tb	6

Ga: 20 mg/kg per day; Gb: 10 mg/kg per day; Gc: 125 mg/day (<20 kg), 250 mg/day (20–40 kg), 500 mg/day (>40 kg); Gd: 125 mg/day (<14 kg), 250 mg/day (14–23 kg), 500 mg/day (>23 kg). Ta: 62.5 mg/day in participants weighing from 10 to 20 kg, 125 mg/day from 20 to 40 kg, and 250 mg/day over 40 kg. Tb: 125 mg/day in subjects weighing less than 25kg, 187.5 mg/day from 25 to 35kg, and 250 mg/day over 35 kg.

listed in Table 26-2. One open study was excluded because no data on the cure rates from each type treatment was provided.²⁵

In most of the studies, the majority of the pathogens belong to the *Trichophyton* species. One of the studies comprises entirely of *Microsporum* species¹² and another had similar portions of *Trichophyton* and *Microsporum* species²⁴. All the studies reported complete cure rate except for one¹⁴ which reported mycologic cure rate. The duration of griseofulvin was 6 or 8 weeks except for one study (12 weeks)¹². The duration of terbinafine in the majority of studies was 4 weeks; one other used 2 to 3 weeks,¹⁹ another used 6 weeks,¹³ and another used 6 to 12 weeks.¹² The mean durations of griseofulvin and terbinafine treatment are 8 and 4 weeks respectively. The dosing of griseofulvin and terbinafine used in the various studies are detailed in the legend of Table 26-2.

The results from the studies are summarized in Table 26-3. In the study by Lipozencic et al.¹² subjects treated with terbinafine were sub-grouped into treatment durations from 6 to 12 weeks. The cure rate at 16 weeks tended to decrease with increased duration of terbinafine treatment paradoxically, although it was not statistically significant. Only the group treated with 6 weeks of terbinafine, which is similar in duration to other studies, was included in the pooled analysis to compare with griseofulvin. The total number of subjects was 2094. The average duration of duration of griseofulvin treatment among the seven studies was 8 weeks and that for terbinafine was 4 weeks (rounded to the nearest week). The time of assessment of cure was 12 weeks for five studies, 16 weeks for one study¹² and 10 for another study.¹³ The cure rates for griseofulvin and terbinafine varied widely, from 39 to 92% and from 45 to 94% respectively.

TABLE 26-3—Results of Studies Comparing Griseofulvin and Terbinafine

Study	Year	N	Assess-ment (week)	Number cured with Griseofulvin	Number not cured with Griseofulvin	Number cured with Terbinafine	Number not cured with Terbinafine	% cure rate of griseofulvin	% cure rate of terbinafine
Haroon ²⁰	1995	105	12	39	10	52	4	79.6	92.9
Memisoglu ²⁴	1999	78	12	17	22	15	24	43.6	38.5
Caceres-Rios ¹⁴	2000	50	12	11	14	19	6	44.0	76.0
Fuller ¹⁷	2001	147	12	40	30	44	33	57.1	57.1
Gupta ¹⁹	2001	100	12	46	4	47	3	92.0	94.0
Lipozencic ¹²	2002	65*	16	25	5	22	13	84	62.1*
Elewski ¹³	2008	1286	10	170	264	384	468	39.2	45.1

*Only the group with terbinafine treatment for 6 weeks is included here.

TABLE 26-4—Pooled Analysis of Studies Comparing Griseofulvin and Terbinafine

	Study	Odds-ratio	95% Confidence Interval		% Weight
1	Haroon ²⁰	3.333	0.973	11.423	9.45
2	Memisoglu ²⁴	0.809	0.328	1.997	14.12
3	Caceres-Rios ¹⁴	4.03	1.201	13.526	9.68
4	Fuller ¹⁷	1	0.52	1.923	19.48
5	Gupta ¹⁹	1.362	0.289	6.426	6.65
6	Lipozencic ¹²	0.338	0.104	1.101	10.04
7	Elewski ¹³	1.274	1.007	1.612	30.57
	Pooled	1.227	0.785	1.919	100

Table 26-4 and Figure 26-1 show the pooled data analysis of the studies and the pooled OR does not significantly favor griseofulvin or terbinafine (1.22 favoring terbinafine; 95% CI=0.785-1.919; p=0.37). The test for heterogeneity is marginally insignificant (p=0.060), suggesting that the effect measures of the studies may not be homogenous.

A further analysis was performed only on the studies with *Trichophyton* species being the predominant

pathogen, (i.e., two studies were excluded).^{12,24} The total number of subjects was 1951 and the results are shown in Table 26-5 and Figure 26-2. The pooled OR favors terbinafine, although the difference did not reach statistical significance (1.49; 95% CI=0.975-2.277; p=0.065). The test for heterogeneity is insignificant (p=0.183), indicating homogeneity of effect measures.

A subgroup analysis was performed to compare the complete cure rates of griseofulvin and terbinafine in *Trichophyton* species (Table 26-6). In the study by Elewski et al.¹³ only data for *T. tonsurans* and *T. violaceum*, which together constitutes 98.4% to 99.4% of all *Trichophyton* species, is available. The total number of subjects was 1388 from four studies and Table 26-6 and Figure 26-3 show the pooled data analysis. The pooled OR significantly favors terbinafine (1.616; 95% CI=1.274-2.051; p<0.001) and the test for heterogeneity is insignificant (p=0.658).

Another subgroup analysis was performed to compare the complete cure rates of griseofulvin and terbinafine in *Microsporum* species (Table 26-3-26-7). In the study by Lipozencic et al.¹² all patients treated with terbinafine (which varies from 6 to 12 weeks) are included. In the study by Elewski et al.¹³ only data for *M. canis*, which constitute 85.4% to 88.6% of all *Microsporum* species, is available.

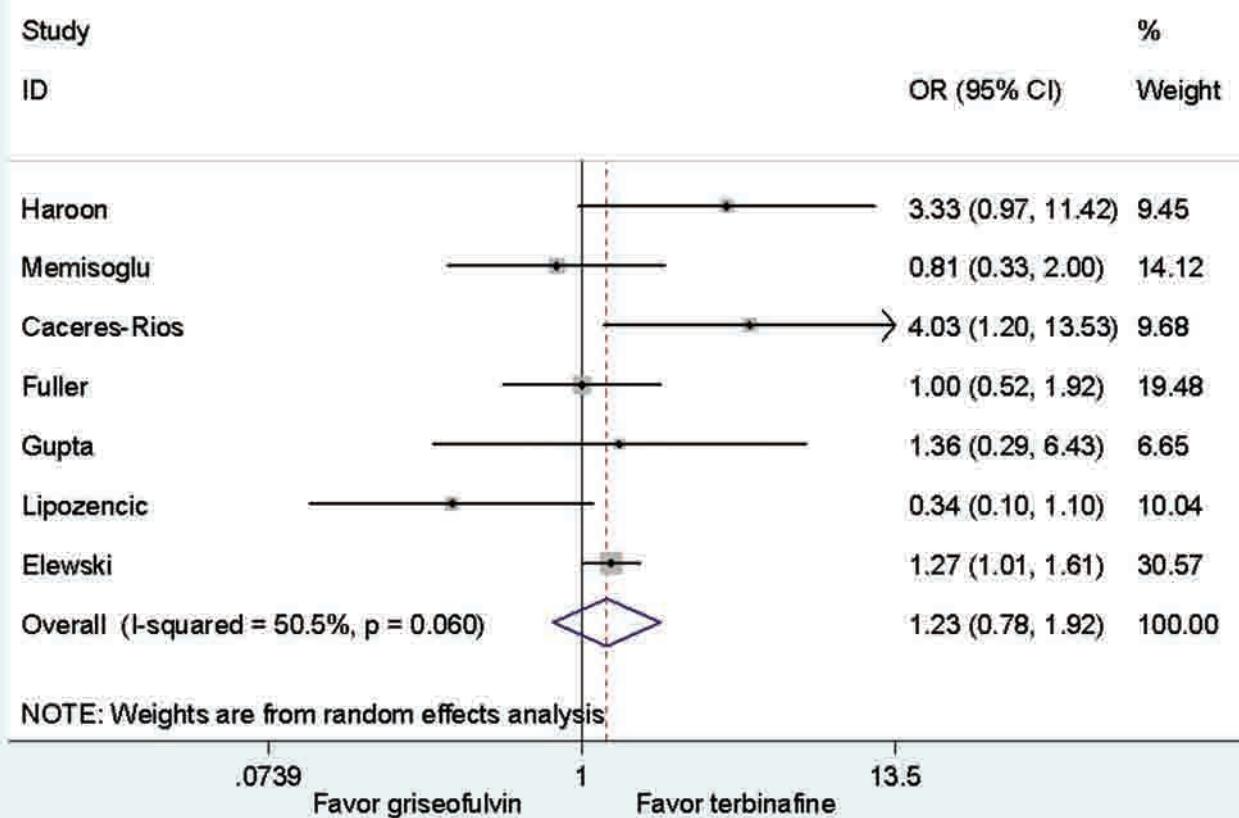
**FIGURE 26-1** Forest plot of studies comparing griseofulvin and terbinafine.

TABLE 26-5—Pooled Analysis of Studies with Predominant ($\geq 65\%$) *Trichophyton* Species Comparing Griseofulvin and Terbinafine

	Study	Odds-ratio	95% Confidence Interval	% Weight
1	Haroon ²⁰	3.333	0.973	11.423
2	Caceres-Rios ¹⁴	4.03	1.201	13.526
3	Fuller ¹⁷	1	0.52	1.923
4	Gupta ¹⁹	1.362	0.289	6.426
5	Elewski ¹³	1.274	1.007	1.612
	Pooled	1.49	0.975	2.277
				100

The total number of subjects was 426 from three studies and Table 26-7 and Figure 26-4 show the pooled data analysis. The pooled OR significantly favors griseofulvin (0.408; 95% CI=0.254–0.656; $p<0.001$) and the test for heterogeneity is insignificant ($p=0.444$).

Adverse Effects

In these studies, the most frequent adverse events caused by terbinafine were gastrointestinal symptoms (such as vomiting, nausea, abdominal pain, and diarrhea) and upper

respiratory tract symptoms (such as infection, nasopharyngitis, cough, and rhinorrhea). Because of concerns about possible leucopenia and hepatotoxicity with the use of terbinafine, serum laboratory analyses were performed in four of the seven studies. No cases of abnormal hematologic indices or liver transaminitis caused by terbinafine were found.

Itraconazole

Comparative Efficacy

Three studies involving 140 subjects comparing itraconazole to griseofulvin and terbinafine were identified.^{19,21,22}

With regards to *Trichophyton* species, a trial which compared the efficacy of griseofulvin to itraconazole, terbinafine, and fluconazole, with 50 subjects in each group, did not demonstrate any significant difference in efficacy between 6 weeks of griseofulvin at 20 mg/kg/day and 2 to 3 weeks of itraconazole at 5 mg/kg/day.¹⁹

Another study involving 60 participants compared 2 weeks of itraconazole (50 to 200 mg/day based on weight) to 2 weeks of terbinafine, did not demonstrate any significant difference in the complete cure rates.²¹

With regards to *Microsporum* species, in a study in which *M. canis* comprised 91.4% of the pathogens, the

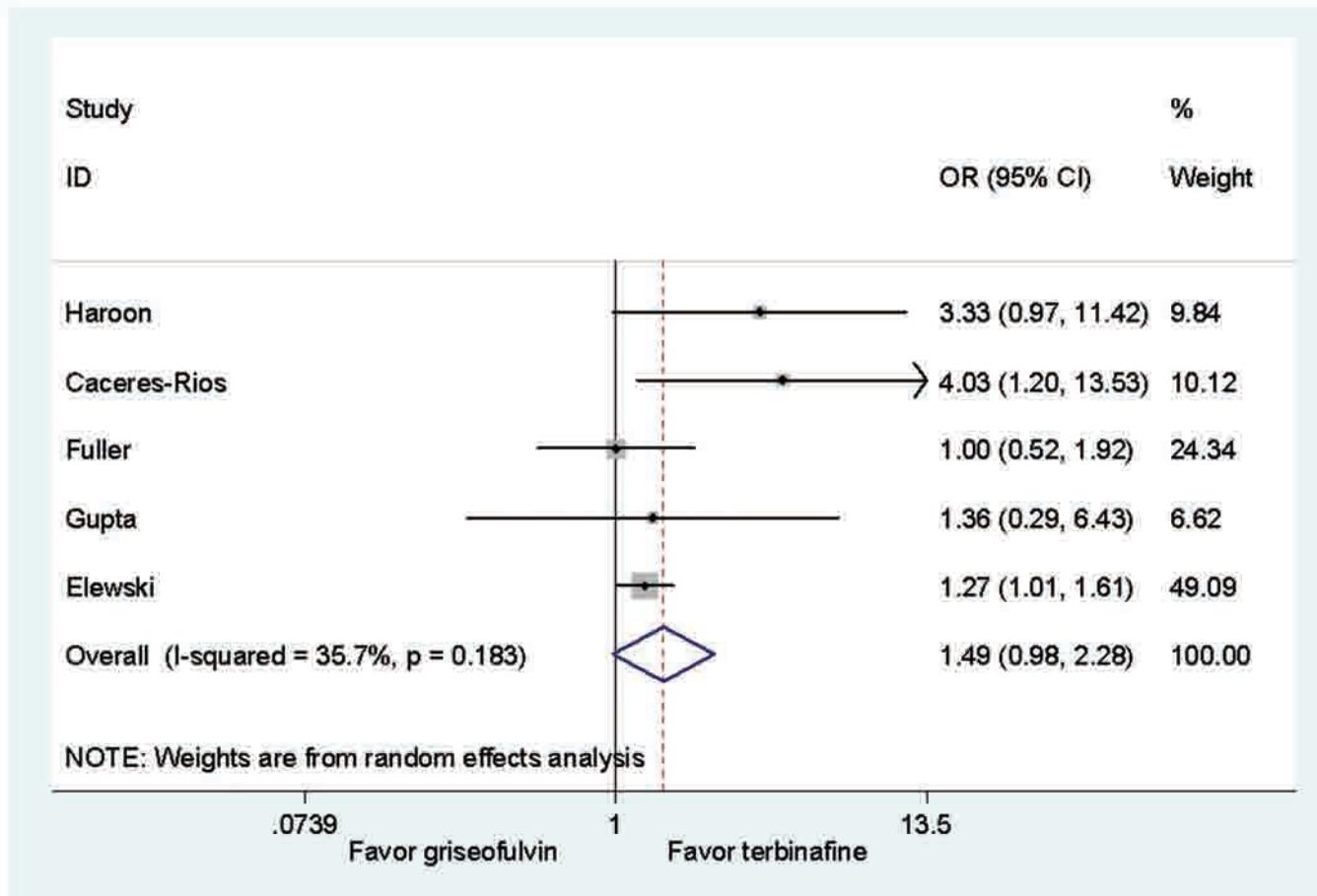


FIGURE 26-2 Forest plot of studies with predominant ($\geq 65\%$) *Trichophyton* species comparing griseofulvin and terbinafine.

TABLE 26-6—Subgroup Analysis of *Trichophyton* Species in Studies Comparing Griseofulvin and Terbinafine

	Study	Cure with griseofulvin	Cure with terbinafine	Odds-ratio	95% Confidence Interval	% Weight
1	Haroon ²⁰	39/49 (79.6%)	52/56 (92.9%)	3.333	0.973, 11.423	3.74
2	Fuller ¹⁷	26/89 (29.2%)	32/88 (36.4%)	1.385	0.737, 2.601	14.28
3	Gupta ¹⁹	46/50 (92%)	47/50 (94%)	1.362	0.289, 6.426	2.36
4	Elewski ^{13*}	128/339 (37.8%)	330/667 (49.5%)	1.614	1.236, 2.108	79.62
	Pooled			1.616	1.274, 2.051	100

*Only figures for *T. tonsurans* and *T. violaceum*, which together constitute 98.4 to 99.4% of all *Trichophyton* species in the study, are available.

complete cure rates of griseofulvin (ultra-microsized, 500 mg/day) and itraconazole (100 mg/day), each given for 6 weeks, were the same at 88% (15/17 and 15/17).²²

Adverse Effects

The most common adverse effects of itraconazole were gastrointestinal symptoms like nausea and abdominal discomfort. There were no severe adverse effects.

Fluconazole

Comparative Efficacy

Four studies involving 1020 subjects comparing fluconazole to griseofulvin were identified.^{15,16,19,28}

In three of the studies, *Trichophyton* species were the predominant (80% and more) pathogens, and there was no significant difference in the efficacy between fluconazole and griseofulvin.^{15,16,19} The first is a trial with 880 participants comparing fluconazole 6 mg/kg per day for 3 weeks, fluconazole 6 mg/kg per day for 6 weeks, and griseofulvin 11 mg/kg per day for 6 weeks.¹⁶ Another trial compared the efficacy of 6 weeks of griseofulvin to 2 to 3 weeks of itraconazole, terbinafine and fluconazole (6 mg/kg/day), with 50 subjects in each subgroup.¹⁹ The third trial involved 40 participants and the efficacy of 4 weeks of fluconazole at 5 mg/kg per day was comparable to 6 weeks of griseofulvin at 15 mg/kg per day.¹⁵

In one study, the pathogens were not reported.²⁸ Griseofulvin at 15 mg/kg/day was compared to fluconazole

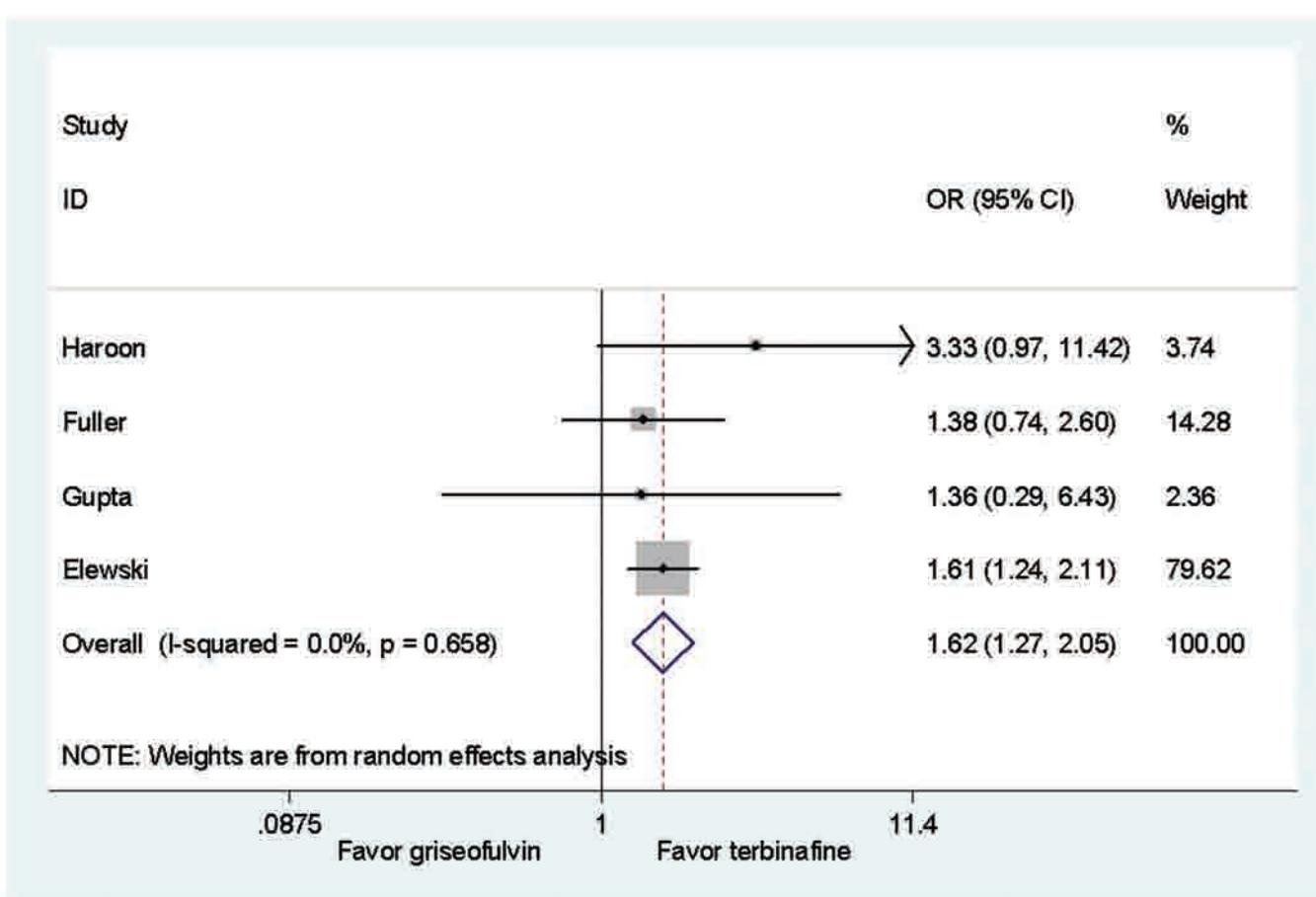


FIGURE 26-3 Forest plot of studies including only subjects infected by *Trichophyton* species.

TABLE 26-7—Subgroup Analysis of *Microsporum* Species in Studies Comparing Griseofulvin and Terbinafine

Study	Cure with griseofulvin	Cure with terbinafine	Odds-ratio	95% Confidence Interval	% Weight
Fuller ¹⁷	5/15 (33.3%)	3/14 (24.4%)	0.545	0.103	2.892
Lipozencic ¹²	25/30 (83.3%)	71/133 [#] (53.3%)	0.229	0.083	0.634
Elewski ^{13*}	36/82 (43.9%)	41/152 (27.0%)	0.472	0.268	0.83
Pooled			0.408	0.254	0.656
					100

[#]All patients treated with terbinafine (varies from 6 to 12 weeks) are included.

*Only figures for *M. canis* are available and included here.

at 6 mg/kg/day, each given to 25 subjects for 2 months. Griseofulvin demonstrated significantly higher clinical cure rate (84% vs 68%) and mycologic cure rate (68% vs 56%).

Adverse Effects

The most common adverse effects were gastrointestinal symptoms (such as abdominal pain and diarrhea), headache, rashes, and liver function test abnormalities. Most of these adverse effects were mild and reversible.

Ketoconazole

Comparative Efficacy

Four studies involving 194 subjects comparing ketoconazole to griseofulvin were found.^{18,23,26,27}

Ketoconazole at doses of 3.3 to 6.6 mg/kg/day for 6 weeks was compared with griseofulvin at 10 to 20 mg/kg/day for 6 weeks in a study consisting 79 subjects.²⁷ The complete cure rate was 48% (16/33) in the ketoconazole group and 54% (25/46) in the griseofulvin group at 12 weeks. Ketoconazole at 200 mg/day was compared to griseofulvin at 250 to 500 mg/day in an earlier trial involving 22 subjects by the same author.²⁶ There were no statistically significant differences between the mycologic cure rates.

Ketoconazole 5 mg/kg/day was compared to griseofulvin 15 mg/kg/day in an open study involving 80 subjects with *Trichophyton* species as the predominant pathogen.¹⁸ 59% (23/40) in the ketoconazole group, and 92% (37/40) in the griseofulvin group had complete cure after 8 weeks of therapy.

Ketoconazole 100 mg/day for 6 weeks was compared to griseofulvin 350 mg/day for 6 weeks in a small study with

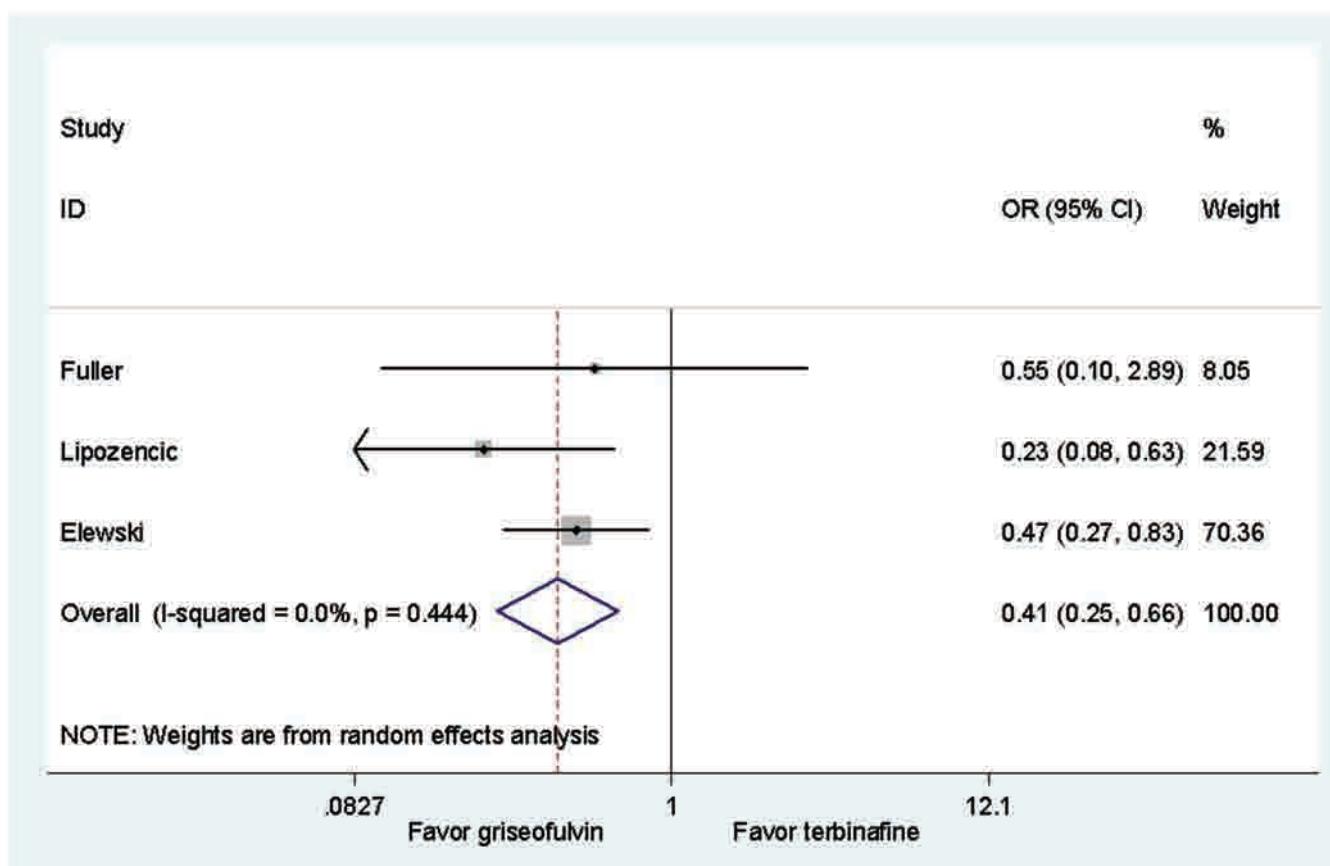


FIGURE 26-4 Forest plot of studies including only subjects infected by *Microsporum* species.

13 subjects.²³ All (8/8) the children in the ketoconazole group, and 80% (4/5) in the griseofulvin group, had clinical improvement and there was no mention of mycologic or complete cure rates.

Adverse Effects

There were no reports of severe adverse effects. Ketoconazole is known for its risk of severe liver toxicity, but there were no reported liver abnormalities among the subjects in these studies. Adverse effects included abdominal pain, nausea, and urticaria.

DISCUSSION

Griseofulvin

Griseofulvin is derived from a species of *Penicillium*, which is a fungus. It exerts its fungistatic effect by arresting mitosis at the metaphase stage of microtubule spindle formation, and thereby stopping cellular division and fungal cell wall synthesis in actively growing fungi. Because of its poor water solubility, it has to be taken with food, and a fatty meal will enhance its absorption. Microsized griseofulvin has a smaller particle size and is better absorbed in the upper gastrointestinal tract. A further increase in absorption is achieved by ultra-microsizing griseofulvin and this allows a reduction in dose by 33 to 50%. The efficacy and safety profile of both formulations microsized and ultra-microsized forms are similar,²⁹ but the latter is not available as a solution.

Griseofulvin is metabolized in the liver and is excreted both in the urine and feces. As it induces cytochrome P450 enzymes in the liver, the metabolism of certain drugs taken concurrently, such as ciclosporin, oral contraceptive pills, and warfarin, can be increased. Griseofulvin is classified in FDA Category C for use in pregnancy and its safety in lactation is undetermined.

Griseofulvin has a narrow spectrum of action, being only effective against the *Trichophyton*, *Microsporum*, and *Epidermophyton* species of dermatophytes. Griseofulvin is licensed for the treatment of tinea capitis in most countries and it has been used as the standard of care to compare with the newer antifungal agents. The advantages of griseofulvin are that it is inexpensive and the suspension formulation enables accurate dosing in children.

Efficacy

The reported efficacy rates of griseofulvin have been highly variable. A meta-analysis published in 2008 involving seven studies (n=438), demonstrated an overall mean mycologic cure rate of 73.4% (+/- 7%) with 4 to 6 weeks of griseofulvin.³⁰ Higher efficacy rates were reported with the use of higher dosages of griseofulvin (more than 18 mg/kg/d). The mean efficacy for *Trichophyton* and *Microsporum* were

67.6% (+/- 9%) in 5 studies (n=396) and 88.1% (+/- 5%) in 2 studies (n=42), respectively.

Dosing

The microsized formulation is administered at a dose of 10 to 25 mg/kg/day and the duration of therapy has generally been 6 to 8 weeks. An unpublished study involving 64 children in a region with high prevalence of *T. violaceum* compared using griseofulvin 10 mg/kg daily for 6 weeks, two doses of 50 mg/kg 1 month apart, and weekly doses of 50 mg/kg for 6 weeks.³¹ The mycologic cure rates between these regimens at 6 weeks and 6 months were not significantly different. In another study involving 35 children in Kenya, the response rate for a single 2 to 3 g dose was 57% and the cumulative response rate after three doses was 91%.³² These studies suggest that intermittent dosing, which enhances compliance, is also effective. These studies did not demonstrate an increased risk of adverse effects at higher dosages of griseofulvin.

Terbinafine

Terbinafine is a tertiary allylamine that inhibits the production of ergosterol, an essential constituent of the fungal cell membrane. It also inhibits squalene epoxidase, causing a toxic accumulation of squalene in the fungal cytoplasm and thereby kills the fungus. In contrast to griseofulvin, its absorption is not altered by food intake. It is very lipophilic and high concentrations are found in hair, stratum corneum, and sebum.³³ Terbinafine also persists in the tissues at fungicidal concentrations after treatment has ceased and cure rates continue to rise for several weeks after termination of therapy.

Eighty percent of the drug is metabolized by cytochrome P450 enzyme in the liver and 20% is excreted in the urine and faeces. The manufacturer does not recommend the use of terbinafine in patients with renal impairment (i.e., creatinine clearance of 50 mL/minute or less) or in those with preexisting liver disease as clearance of the drug may be decreased substantially. The level of terbinafine is decreased by rifampicin, a strong inducer of cytochrome P450 enzyme. Terbinafine in turn increases the levels of paroxetine, venlafaxine, and tricyclic antidepressants when they are used concurrently. Terbinafine is classified in FDA Category B for use in pregnancy and its use in lactation is contraindicated.

Terbinafine has demonstrated a good safety profile, and therefore, represents a good alternative to griseofulvin for treatment of tinea capitis in children. Its advantage is its shorter duration of treatment of about 4 weeks, in contrast to 6 to 8 weeks for griseofulvin. On the other hand, it is more costly and is not available in suspension or liquid formulation. Terbinafine hydrochloride oral granules have recently been developed as a new pediatric formulation consisting of miniature granules that can be sprinkled over food and swallowed easily.¹³ The granules are approximately 2.1 mm

in diameter and are film coated for masking the taste, facilitating its administration to children. This formulation is currently not widely available.

Meta-analysis of seven RCTs did not reveal any significant difference in efficacy between griseofulvin and terbinafine in the treatment of tinea capitis. In the pooled analysis of five studies in which *Trichophyton* species were the predominant (65% and more) pathogenic dermatophyte, terbinafine appeared to be more efficacious than griseofulvin. Subgroup analysis revealed that terbinafine was more efficacious than griseofulvin in treating tinea capitis caused by *Trichophyton* species. On the other hand, the analysis suggests that griseofulvin was more efficacious than terbinafine in treating tinea capitis caused by *Microsporum* species.

Several clinical applications can be derived from the above results. If clinical findings suggesting *Microsporum* species is the infecting dermatophyte, such as the presence of fluorescence under Wood's lamp, and having a pet which may have transmitted *M. canis*, empirical use of griseofulvin is recommended. In the absence of these features and in populations which *Trichophyton* species are the predominant pathogens causing tinea capitis, empirical use of terbinafine is recommended if cost is not an issue. When faster PCR-based diagnostic tests become commercially available,⁸ the identification of infecting species will enable a more targeted and effective use of anti-fungal agents.

Itraconazole

Itraconazole, a synthetic triazole derivative, is an azole antifungal agent and it is available in tablet and solution form. Its fungistatic activity is caused by the inhibition of the cytochrome P450-dependent synthesis of ergosterol, which is a vital component of fungal cell membranes. It is metabolized predominantly by the cytochrome P450 enzyme and the half-life of the drug is increased in liver impairment. Although approximately 40% of the drug is excreted in the urine as inactive metabolites, adjustment in dosage is not necessary in renal impairment.

Azoles are substrates and inhibitors of cytochrome P450 3A4 isoenzyme and P-glycoprotein (a plasma membrane transporter responsible for metabolism in intestinal enteroctyes) and they decrease the metabolism of multiple drugs.³⁴ Itraconazole is classified in FDA Category C for use in pregnancy and its use in breast-feeding mothers is contraindicated.

Some RCT evidence suggests that oral itraconazole is effective and safe when used for 2 to 6 weeks in the treatment of tinea capitis. The few studies available show that itraconazole is as effective as griseofulvin when used for 2 weeks against *Trichophyton* species and when used for 6 weeks against *M. canis*. The availability in both tablet and liquid formulation enables accurate and convenient dosing in children.

Fluconazole

Fluconazole is the first of the new subclass of synthetic triazole antifungal agents and it is available as tablet and suspension forms. Fluconazole is a highly selective inhibitor of the fungal cytochrome P450-dependent enzyme lanosterol 14- α -demethylase which converts lanosterol to ergosterol. The drug is cleared primarily by renal excretion and dose adjustment may be required in patients with renal impairment. Like other azoles, it decreases the metabolism of many drugs and increases their plasma concentration.³² Fluconazole is classified as FDA category C for use in pregnancy and as it is secreted in human milk at concentrations similar to plasma, its use in breast-feeding mothers is not recommended.

In studies with predominance of *trichophyton* species (80% and more), fluconazole used for 3 to 6 weeks is as effective as griseofulvin and is safe for the treatment of tinea capitis. The availability in both tablet and liquid formulation enables accurate and convenient dosing in children.

Ketoconazole

An occasional but serious adverse effect of ketoconazole is idiosyncratic hepatic toxicity (primarily hepatocellular type) and there have been rare fatalities from severe hepatic necrosis. The limited evidence available suggests that griseofulvin may be better than ketoconazole in the treatment of tinea capitis. Due to these reasons, ketoconazole is seldom used for tinea capitis, especially when safer azole compounds such as itraconazole and fluconazole are currently available.

Adjunctive Therapy

Topical Anti-Fungal Agents

Selenium sulfide shampoo was shown to be an effective adjunctive therapy to griseofulvin for the treatment of tinea capitis in a randomized controlled trial (Allen 1982). Ninety four percent of children with *T. tonsurans* infections treated with daily oral griseofulvin and selenium sulfide shampoo twice weekly demonstrated mycologic cure at 4 weeks compared to 75% of children who were treated with griseofulvin alone, or in combination with either a bland shampoo or topical clotrimazole. Another RCT of 54 patients with *T. tonsurans* tinea capitis treated with griseofulvin showed that twice weekly selenium sulfide shampoo was superior to nonmedicated control shampoo in achieving a faster mycologic cure.³⁵ There was, however, no difference between 2.5% and 1% selenium sulfide preparations in the time required to produce a negative culture and the authors concluded that commercially available 1% selenium sulfide shampoo is equally effective and less expensive compared to the 2.5% preparation.

An open study evaluated daily ketoconazole 2% shampoo for 8 weeks as a monotherapy for the treatment of *T. tonsurans* tinea capitis.³⁶ Six of the 15 children (40%) had negative cultures after 2 weeks but one child relapsed at the fourth week. The rest of the five children (33%) remained culturally negative for 12 months post-treatment.

A RCT was performed in Zimbabwe that compared 6 weeks of Whitfield's ointment (6% benzoic acid and 3% salicylic acid) with miconazole cream in the treatment of tinea capitis. There was no significant difference in cure rates between Whitfield's ointment and miconazole cream and the combined mycologic cure rate of both medications was 67% (22/33).³⁷ Another RCT was performed in Tanzania to access the efficacy of two months of Triclosan bar soap in comparison with regular soap against superficial mycoses (tinea capitis, pityriasis versicolor, tinea corporis, and tinea pedis).³⁸ No significant benefit was found with the addition of Triclosan to bar soap and the average mycologic cure rate of tinea capitis for both the Triclosan and placebo groups were 21.8%.

With regards to the management of asymptomatic carriers, there were no RCTs found. A nonrandomized study comparing different shampoos in carriers found that the mycologic cure rates for povidone-iodine shampoo, econazole shampoo, 2.5% selenium sulphide shampoo, and control shampoo were 94%, 47%, 50%, and 50% respectively.³⁹

In summary, There is limited RCT evidence to support the use of selenium sulfide shampoo as an adjuvant topical therapy in the treatment of tinea capitis. The main purpose of topical antifungal therapy is to achieve a faster mycologic cure so as to reduce the transmission of the disease. Although there is only limited evidence to support the treatment of carriers, it is reasonable to use these topical agents, in particular povidone-iodine shampoo, to reduce the carrier rate and to prevent carriers from getting infected subsequently.

Corticosteroids for Kerions

There were two RCTs that found that the addition of oral prednisolone to griseofulvin did not confer additional benefits or result in improved cure rates.^{40,41} Another RCT also did not find adjuvant intralesional corticosteroid beneficial for patients with kerions treated with griseofulvin.⁴²

CONCLUSION

Terbinafine, itraconazole, and fluconazole demonstrated comparable efficacy to griseofulvin in the treatment of tinea capitis. Terbinafine is more efficacious against *Trichophyton* species compared to griseofulvin, while evidence suggests that the converse is true with regard to *Microsporum* species. Griseofulvin, terbinafine, itraconazole, and fluconazole demonstrated good safety profiles when used in the treatment of tinea capitis. Griseofulvin has the advantages of a long and excellent safety record, wide availability, and

low cost. The newer anti-fungal agents, on the other hand, provide the advantage of a shorter duration of treatment and thereby help improve compliance.

As an adjuvant therapy to griseofulvin, selenium sulphide shampoo may shorten the time to mycologic cure and thereby reduce transmission. In the treatment of kerions with griseofulvin, oral and intralesional corticosteroids do not provide additional benefit.

What We Know

- RCT evidence indicates that terbinafine is more efficacious than griseofulvin in treating tinea capitis caused by *Trichophyton* species.
- RCT evidence suggests that griseofulvin is more efficacious than terbinafine in treating tinea capitis caused by *Microsporum* species.
- Some RCT evidence suggests that itraconazole is as efficacious as griseofulvin in the treatment of tinea capitis.
- RCT evidence indicates that fluconazole is as effective as griseofulvin in the treatment of tinea capitis although this may only be applicable to *Trichophyton* species.
- Griseofulvin, terbinafine, itraconazole, and fluconazole demonstrated good safety profiles when used in the treatment of tinea capitis.
- Limited RCT evidence suggests that selenium sulphide shampoo shortens the time to mycologic cure in patients treated with griseofulvin.
- Oral and intralesional corticosteroids do not provide additional benefit to griseofulvin in the treatment of kerion.

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Treatment of Tinea Versicolor

27

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INTRODUCTION

Tinea versicolor (TV) is a superficial fungal skin infection caused by *Malassezia* spp. It most commonly affects the upper body, arms, neck, and face as round or oval hyperpigmented or hypopigmented macules with overlying flaky scale (Figure 27-1). Although some patients experience mild pruritus, most are asymptomatic. TV is responsive to a multitude of therapies including several oral antifungals, various formulations of topical antifungals, keratolytic agents, and nonspecific antimicrobial agents. As recurrence is common, prophylactic regimens are often required.

The optimal therapy has a high cure rate; minimal side effects; a very low or prolonged time to relapse, and is cosmetically acceptable to the patient. The questions and responses that follow attempt to provide the best evidence available supporting various treatment approaches to TV, relying on data from randomized-controlled trials (RCTs). Where RCTs are unavailable, data from longitudinal observational studies will be discussed, recognizing that conclusions from this type of evidence are more limited.

EPIDEMIOLOGY

TV is a disease of teenagers and young adults that affects men and women equally within all socioeconomic groups. When children and older adults are affected, it is usually within the setting of other endogenous and exogenous predisposing factors. Endogenous factors predisposing individuals to TV include malnutrition, use of oral contraceptives, use of systemic immunosuppressants including corticosteroids, immune deficiency disorders including acquired immune deficiency syndrome (AIDS), and hyperhidrosis.¹ Exogenous factors include tropical climates, occlusion by clothing, creams, or lotions, and hospitalization.¹ Hygiene is not an important contributor to the development of TV. The significant importance of climate is highlighted by the 1% prevalence of TV in Scandinavia versus 50% prevalence in many tropical countries.

ETIOLOGY/DIAGNOSIS

Yeasts of the genus *Malassezia* are the cause of TV. Of the various species, *Malassezia globosa*, *M. sympodialis*, and *M. furfur* are the most common species and likely cause of TV.² Ninety to 100% of individuals carry *Malassezia* species as part of their normal flora, however, TV only develops when the organism converts from a yeast to the mycelia form and infects the stratum corneum.² The cause of pigmentary changes is incompletely understood, but is hypothesized to be caused by some combination of inflammation, alteration of melanin production, melanocyte damage, and abnormal melanosome transfer to keratinocytes.³ Azelaic acid, lipoxygenase, and tryptophan metabolites produced by the fungus are currently under investigation as causative factors for the above changes.³

Tinea versicolor is diagnosed clinically by the appearance of round to oval macules in mostly seborrheic areas. The macules may be pink, tan, brown, black, or hypopigmented, and smooth or covered with fine scale. Wood's light (365 nm filtered ultraviolet light) will produce a bright yellow or gold fluorescence in approximately one-third of cases.¹ Skin scrapings or tape strippings from the



FIGURE 27-1 Tinea versicolor commonly affects the upper body, arms, neck, and face.

edge of scaly lesions will reveal the characteristic “spaghetti and meatballs” appearance of spores and hyphae under light microscopy, after incubation in potassium hydroxide (KOH). Skin biopsy is generally not necessary, but will reveal hyphae and budding yeast within the stratum corneum after staining with periodic acid-Schiff or methenamine silver.

SEARCH METHODOLOGY

In general, the approach used was to restrict searches in Medline to RCTs or randomized longitudinal series, as well as systematic reviews of tinea versicolor treatment in the English literature. Open-label, long-term follow-up from RCTs is provided where applicable. We also conducted hand searches of bibliographic references. Retrospective studies were not included.

Is one oral agent more effective than others for tinea versicolor?

Seven studies have directly compared the efficacy of oral therapies for TV. Kose compared fluconazole 300 mg twice daily to itraconazole 400 mg twice daily for 2 weeks in 64 patients.⁴ Patients with extensive or recurrent TV were randomly assigned one of the above regimens. Clinical cure was defined as resolution of scaling, pigmentary changes, and pruritus. Mycologic cure was defined as a negative KOH and Wood's lamp examination. At completion of the study, 80% of the patients treated with fluconazole, 74% of the patients treated with itraconazole were clinically cured, and 88% in the fluconazole group and 80% in the itraconazole group were cured. The difference was not considered clinically significant.

Single dose fluconazole (400 mg) versus single dose itraconazole (400 mg) was compared by Partap et al. in a RCT of 40 consecutive patients with over 15% skin surface involvement.⁵ Clinical cure was defined as resolution of pigmentary changes at 8 weeks. Mycologic cure was defined as negative cultures at weeks 2 and 8. Relapse was defined as reappearance of clinical signs or a positive culture after initial improvement. Pigmentary changes resolved in 20% of the fluconazole group versus 5% in the itraconazole group (not statistically significant). Cultures were negative in 10% at 2 weeks and 65% at 8 weeks in the fluconazole group versus 30% and 20% respectively in the itraconazole group. Thirty-five percent of the patients treated with fluconazole relapsed versus 60% in the itraconazole group, which was statistically significant ($p<0.05$).

Two regimens of fluconazole (450 mg single dose and 300 mg two doses given one week apart) were compared to itraconazole 200 mg daily for 7 days by Montero-Gei et al.⁶ Ninety patients were evaluated in a multicenter open label RCT. Clinical cure was defined as an absence of erythema, scaling, or pigmentary changes at day 60. Mycologic cure

was defined by negative skin scrapings on microscopy. Clinical cure was achieved in 52% of the fluconazole single dose group, 70% with two doses of fluconazole, and 74% with itraconazole. The difference between two doses of fluconazole and 1 week of itraconazole were not statistically significant. Mycologic cure between two doses of fluconazole and itraconazole were also not statistically significant (77% and 78%, respectively).

Itraconazole and ketoconazole were compared by Shermer et al. in a single center open label RCT.⁷ Itraconazole was given to 35 patients at 200 mg daily for 1 week and to 34 patients at 100 mg daily for 2 weeks. Thirty-six patients received ketoconazole at 400 mg per day 7 days apart. Mycologic cure at 4 weeks was assessed and cure was obtained in 85% of those receiving itraconazole 200 mg daily for 1 week, 81% of those receiving itraconazole 100 mg for 2 weeks; and 83% of those receiving 2 doses of ketoconazole 400 mg 7 days apart. The differences were not statistically significant. Clinical cure was not assessed.

Bhogal et al. compared four regimens of fluconazole and ketoconazole in 180 patients in an open RTC⁸: ketoconazole 400 mg once (group 1), ketoconazole 200 mg daily for 10 days (group 2), fluconazole 400 mg once (group 3), and fluconazole 150 mg weekly for 4 doses (group 4). Follow-up examinations were performed at 2 and 4 weeks and then at 3, 6, and 12 months after treatment. KOH and Wood's lamp examinations were performed at each visit. At 4 weeks post-treatment, 66%, 73.3%, 80%, and 59% of patients were clinically cured. However, at 12 months post-treatment, no patients in group 3 relapsed, whereas group 1 had more relapses than any other group. The authors concluded that fluconazole 400 mg in one dose was the most effective treatment for TV.

Ketoconazole (400 mg repeated in 1 week) was compared to fluconazole (300 mg repeated in 1 week) by Farschian et al. in an open RCT.⁹ 128 patients were recruited into the study with 100 completing it. Patients were assessed by clinical examination, potassium hydroxide smears, and Wood's lamp at the beginning of the study, immediately after completing therapy, and at 4, 8, and 12 weeks after initiating therapy. At week 8, 90% of those in the fluconazole group and 88% of those in the ketoconazole group were mycologically cured (negative KOH). At week 12, 82% of the fluconazole group, and 78% of the ketoconazole group were mycologically cured. These differences were not statistically significant.

Similarly, no statistically significant difference was found between fluconazole (300 mg in 2 doses, 2 weeks apart) and ketoconazole (400 mg as a single dose) by Yazdanpanah et al.¹⁰ Patients were evaluated for the extent of lesions, hyperhidrosis, and greasiness of the skin at the initial visit and at 1 month after completion of therapy. Mycologic examination (10% KOH preparation and Wood's lamp examination) was only performed if there was a question about the diagnosis at the initial visit or about the patient's cure at the final visit. In this open RCT, ninety patients were recruited

with 30 patients being eliminated from the study, as they were lost to follow-up or utilized topical agents in addition to the study drugs. Twenty-two of 27 (81.5%) patients in the fluconazole group and 29 of 33 (87.9%) patients in the ketoconazole group improved at the study's conclusion.

No studies were found evaluating the efficacy of systemic terbinafine or griseofulvin; however, they are stated to be ineffective in the treatment of TV.¹

CONCLUSION

Azole antifungals are effective against TV. There is insufficient evidence to recommend any one azole over others. There is no data to support or refute the efficacy of oral terbinafine or oral griseofulvin in the treatment of TV, but they are felt to be ineffective as oral agents.

Is one topical agent more effective than others for tinea versicolor?

Multiple topical agents are effective in the treatment of TV with diverse mechanisms of action. Nonspecific

antifungal agents that work by removing infected stratum corneum or altering cell turnover rates include selenium sulphide, propylene glycol, Whitfield's ointment (benzoic acid 12% and salicylic acid 6%), sulphur and salicylic acid, povidone-iodine, and benzoyl peroxide. Specific antifungal agents that directly act against the fungus include haloprogin, zinc pyrithione, tolccilate, ciclopirox olamine, griseofulvin, terbinafine, and the azole antifungals. None have been compared head-to-head, however, efficacy in RCTs compared to placebo are available (Table 27-1).

CONCLUSION

Many topical agents appear effective in treating TV. Although there is insufficient comparative evidence to recommend one topical agent over others, only a few agents (i.e., selenium sulfide 2.5% lotion, terbinafine 1% solution, ketoconazole 2% cream, ketoconazole 2% shampoo, econazole nitrate 1% cream, clotrimazole 1% cream and clotrimazole 1% solution) have established efficacy in randomized placebo-controlled trials. It is prudent to utilize these more established agents over the less studied alternatives.

TABLE 27-1—Randomized, Placebo-Controlled, Double-Blind Studies of Topical Agents for Tinea Versicolor

Reference	Regimen	Number of Patients	Clinical Cure (%)	Mycologic Cure (%)
11	Selenium sulfide 2.5% lotion once-daily for 1 week	48	NR*	39(81)
	Selenium sulfide 2.5% lotion + 0.2% colorants once daily for 1 week	38	NR	27(71)
	Vehicle + -.2% colorants once daily for 1 week	46	NR	7(15)
12	Terbinafine 1% solution twice daily for 1 week	76	55 (72)	62 (81)
	Placebo twice daily for 1 week	34	9 (26)	14 (41)
13	Econazole nitrate 1% cream once daily for 2-3 weeks	67	NR	53 (79)
	Placebo once daily for 2-3 weeks	59	NR	37 (63)
14	Clotrimazole 1% solution once daily for 2 weeks	116	96 (83)	96 (83)
	Vehicle once daily for 2 weeks	107	68 (64)	68 (64)
	Clotrimazole 1% cream once-daily for 2 weeks	10	8 (80)	8 (80)
15	Vehicle once-daily for 2 weeks	8	3 (38)	3 (38)
	Ketoconazole 2% cream once daily for 11-22 days (mean 14 days)	51	34 (67)	43 (84)
	Placebo daily	50	11 (22)	11 (22)
16	Ketoconazole 2% shampoo on day one and placebo once daily for next 2	103	71 (69)	79 (78)
	Ketoconazole 2% shampoo once-daily for 3 days	106	77 (73)	89 (84)
	Placebo once-daily for 3 days	103	5 (5)	11 (11)

*Not reported

Is systemic therapy more effective than topical therapy for tinea versicolor?

Systemic therapy is sometimes recommended above topical therapy when TV involves a large area of skin or when the disease is recurrent; however, only one study addresses the effectiveness of oral versus systemic therapy. In an open, randomized trial, del Palacio Hernanz et al. compared itraconazole 200 mg daily for 5 days (20 patients) with 2.5% selenium sulfide shampoo (20 patients) daily for 7 days.¹⁷ Three weeks after completion of therapy 20% of patients in the itraconazole arm achieved clinical and mycologic cure versus 45% of patients in the selenium sulfide arm. Interestingly, despite the lower cure rate, all 20 patients (100%) in the itraconazole group and 10 of 20 patients (50%) in the topical group stated they preferred oral over topical therapy.

CONCLUSION

In the only study directly comparing systemic and oral therapy for TV, topical selenium sulfide shampoo appears more effective than oral itraconazole. There is no evidence by comparative trials to recommend the use of systemic therapy over topical therapy based on the extent or recurrence of TV. Therefore, the choice of systemic versus topical therapy for TV should weigh more heavily on individual patient characteristics (patient preferences, ability to apply medication, cost, potential drug interactions, etc.) than the extent or persistence of the disease.

What are effective approaches to prevent recurrence of tinea versicolor?

As stated in the introduction, multiple intrinsic and extrinsic factors predispose individuals to TV, and therefore, patients often require prolonged or recurrent therapy to maintain improvement. Indeed, recurrence rates as high as 60% at 1 year and 80% at two years have been reported after treatment of TV.¹⁸ Despite the high recurrence rates, studies of TV therapies rarely extend beyond 4 weeks. Three studies address prophylactic treatment of TV.^{18–20}

In an open label study, Rausch and Jacobs treated 22 patients with ketoconazole 400 mg by mouth once.¹⁹ All patients achieved mycologic cure (negative Wood's lamp and KOH examination) at 1 month. Patients were then continued on ketoconazole 400 mg by mouth once monthly. Follow-up of 20 of these patients ranged from 4 to 15 months (mean 8.2 months), during which one had a recurrence. Faergemann and Djärv followed patients for 11 months on ketoconazole 200 mg/d for 3 consecutive days, once per month and had a similar low rate of recurrence.²⁰

Faergemann et al. evaluated itraconazole prophylaxis in a 6-month multicenter RCT.¹⁸ In the open, active

treatment phase itraconazole 200 mg was given daily to 238 patient followed by 4 weeks without active therapy. Ninety-two percent (205 patients) were clinically improved and mycologically cured (negative KOH preparation). In the double-blind prophylactic treatment phase, patients were randomized to itraconazole, 200 mg (102 patients), or placebo (99 patients) twice on 1 day per month for 6 consecutive months. At the trial's conclusion 88% of the patients receiving itraconazole remained mycologically negative versus 57% of those in the placebo arm ($P<0.001$).

Topical therapies and oral fluconazole have not been evaluated as prophylactic therapies in a RCT, however, one open-label study did evaluate relapses at 2 years following initial clinical and mycologic cure with selenium disulfide suspension.²¹ In this study, Hersle et al. achieved clinical and mycologic cure (negative KOH preparation) 4 weeks after one application of selenium disulfide suspension. Twenty-nine patients were then treated prophylactically one night every third month for 1 year and 30 patients received no further therapy. At 24 months, 53% of those who did not receive prophylaxis relapsed versus 14% in the prophylaxis group.

CONCLUSION

Prophylactic therapy with oral itraconazole (400 mg/d) or ketoconazole (400 mg/d or 200 mg/d for three consecutive days) once monthly appear to be effective prophylactic regimens. There is not enough evidence to support prophylaxis with any topical agents or oral fluconazole at this time.

What is the optimal dosing regimen for oral ketoconazole?

Ketoconazole was introduced at 200 mg daily for 4 weeks, however, subsequent studies have found shorter regimens to be effective. Four studies directly compare various regimens of oral ketoconazole, with dosing ranging from one 400 mg dose of ketoconazole to five weeks of daily therapy.^{22–25}

The first comparative trial was an open-label trial of 64 patients that compared ketoconazole 200 mg daily for 3 weeks (32 patients) versus 5 weeks (32 patients).²² Clinical and mycologic cure were assessed at 2 weeks after treatment. Eighty-one percent of those receiving 3 weeks versus 100% of those receiving 5 weeks of ketoconazole were clinically and mycologically cured. In contrast, a double-blind, randomized trial Hay et al. compared ketoconazole 200 mg daily for 5, 15, and 25 days and found no statistical significance in cure with length of therapy.²³ Thirty-six patients were enrolled in the study with 12 patients randomized to each dosing regimen. To maintain blinding in patients with regimens less than 25 days, placebo was provided to day 25 after completing the active treatment phase. At 28 days after therapy 83%, 75%, and 67% of those who received

5 days, 15 days, and 25 days of ketoconazole were clinically and mycologically cured. The differences were not statistically significant. An even shorter regimen was evaluated in a double-blind, randomized, placebo-controlled trial by Zaias.²⁴ Fifty-nine patients were randomized to receive ketoconazole 200 mg daily for 10 days, ketoconazole 200 mg daily for 5 days (followed by 5 days of placebo), or 10 days of placebo. Patients were assessed clinically and mycologically (KOH exam) 30 days after therapy. Ninety percent, 84%, and 17% of those receiving ketoconazole for 10 days, 5 days, or placebo, respectively, were clinically and mycologically cured. There was no significant difference between ketoconazole groups, but both were statistically better than placebo.

Most recently, Fernandez-Nava et al. compared ketoconazole 400 mg once (60 patients) with ketoconazole 200 mg daily for 10 consecutive days (60 patients).²⁵ The study was carried out in the Philippines where the relative humidity ranged from 74%-77% during the study period. All patient had 25-50% body surface area affected as determined by physical examination, KOH, and Wood's lamp examination. At 1 month after therapy, 42% of those receiving ketoconazole 400 mg once and 51% of those receiving ketoconazole 200 mg daily for 10 days were mycologically cured (defined as a negative KOH and Wood's lamp examination). The difference was not statistically significant.

CONCLUSION

Ketoconazole appears effective in various regimens ranging from 400 mg once to 200 mg daily for 5 to 35 days. There is insufficient evidence to recommend longer courses of ketoconazole over very short courses ketoconazole.

What is the optimal dosing regimen for oral itraconazole?

Dosing studies of itraconazole have looked at frequency of administration (once daily versus twice daily); the minimal effective cumulative dose; and the optimal length of therapy for cure of tinea versicolor. All comparative studies have been open-label and small, involving 50 or less total patients for comparison. The optimal minimum total cumulative dose of itraconazole is generally believed to be one gram based on data from clinical experience and placebo-based studies, but not comparative studies.²⁶

The daily frequency of itraconazole administration to reach one gram has been evaluated in three open-label, randomized trials comparing twice daily to once daily dosing. Panconesi et al. compared itraconazole 200 mg daily in a single dose for 5 days (15 patients) versus itraconazole 200 mg daily in a divided dose for 5 days (15 patients).²⁷ One hundred percent of patients were cured

in both groups. Simoni et al. had similar results.²⁸ Fifteen patients received itraconazole 200 mg daily in a single dose and 15 patients received itraconazole 200 mg daily in a divided dose for 5 days. Four weeks after treatment, 100% of the patients in both groups were clinically and mycologically cured. Again, divided versus once daily administration had no effect on efficacy in a study by Fioroni et al. comparing 13 patients on itraconazole 200 mg as a single daily dose versus 15 patients on itraconazole 200 mg daily as a divided dose.²⁹ Both groups were 100% clinically and mycologically at 4 weeks after the end of treatment.

Three studies have compared itraconazole's efficacy when one total gram is administered over 5 days versus 10 days.^{26,30,31} Del Palacio-Hernandez et al. compared itraconazole 200 mg daily for 5 days (15 patients) versus itraconazole 100 mg daily for 10 days (15 patients) in a randomized open-label study.³⁰ Patients were considered cured if they had no or mild residual lesions at 3 weeks post-treatment and a negative KOH examination. Ninety-three percent and 87% of the patients were cured in the 200 mg and 100 mg itraconazole daily groups respectively. The same dosing schedules were compared by Estrada.³¹ Twenty-two patients were prescribed itraconazole 200 mg daily for 5 days and 20 patients were prescribed itraconazole 100 mg daily for 10 days. Patients were assessed by Wood's lamp examination and KOH at the end of treatment. Seventy-five percent of those prescribed itraconazole 200 mg daily were mycologically cured versus 95% of those on 100 mg daily—the difference was not statistically significant. Clinical cure and long-term follow-up were not reported. Lastly, Massone et al. assessed patients for clinical and mycologic cure 4 weeks after beginning treatment.³² One hundred percent (10 of 10 patients) of those receiving 100 mg daily for 10 days were cured versus 80% (8 of 10 patients) receiving 200 mg daily for 5 days.

The one gram cumulative dose has been tested against both greater and lesser doses in four randomized, open-label studies—none of them showing clinically significant differences. Two studies evaluated greater cumulative doses.^{33,34} Cuce et al. compared itraconazole daily for 7 days (21 patients) with itraconazole 200 mg daily for 5 days (15 patients).³³ Patients were evaluated by clinical examination, Wood's lamp examination, and KOH at 35 days from the start of therapy. Ninety percent of those in the 5-day group and 95% of those in the 7-day group were clinically and mycologically cured. There was no statistically significant difference in cure rates. Galimberti et al. compared the same regimens: itraconazole 200 mg daily for 5 days (13 patients) or itraconazole 200 mg daily for 10 days (15 patients).³⁴ Cure was defined as the absence of clinical symptoms and a negative culture result. Twenty-eight days post-treatment, 86.7% of those in the 7-day group and 77% of those in the 5-day group were cured. The difference was not statistically significant. Lower cumulative doses have also been compared in two

studies.^{35,36} Morales-Doria compared itraconazole 100 mg twice daily (1 gram cumulative dose) to itraconazole 100 mg once daily (500 milligrams cumulative dose).³⁵ Twenty-four patients received 1 gram total dose and 23 received 500 milligrams total dose. Mycologic cure was assessed by tape-stripping and light microscopy, however, clinical cure was not assessed. Twenty-eight days after completion of therapy, 96%, and 100% of patients were mycologically cured in the 1-gram group and 500-milligram group, respectively. Kose et al. compared one 400 mg dose (24 patients) versus a 7-day 200 mg daily dose (26 patients) of itraconazole.³⁶ Patients were evaluated by clinical examination, KOH preparation, and Wood's lamp examination. Six weeks after starting therapy 75% and 83% of patients in the one-day group were clinically and mycologically cured, respectively.^{36,37} Eighty-one percent and 88% of patients in the 7-day group were clinically and mycologically cured, respectively.^{36,37} The differences were not statistically significant.

CONCLUSION

Itraconazole is highly effective at 1-gram total dose whether given over 5 days or 10 days once daily or as a divided daily dose. Higher total cumulative doses have not been shown to be superior. On the other hand, there is evidence that lower doses (i.e., 400 mg once or 500 mg total dose given over 5 days) may be as effective as the standard 1-gram cumulative dose.

What is the optimal dosing regimen for oral fluconazole?

As fluconazole is highly concentrated and persistent within the stratum corneum, once weekly dosing is typically prescribed for superficial fungal infections including TV.³⁸ Two studies have compared four dosing schedules for fluconazole.^{6,39} Amer et al. compared fluconazole 150 mg weekly for four doses, fluconazole 300 mg weekly for four doses, and a single dose of fluconazole 300 mg repeated at 2 weeks.³⁹ Six hundred and three patients were randomized to each schedule. A clinical and mycologic (KOH preparation) assessment was performed weekly during the treatment phase, wherein patients only received their scheduled dose if they showed clinical or mycologic evidence of residual TV. Patients were assessed for mycologic cure at 28 days after completing therapy. Clinical cure was not reported. At the final evaluation, 78% (161/207 patients) in the group receiving fluconazole 150 mg weekly, 93% (178/190 patients) in the group receiving fluconazole 300 mg weekly, and 87% (179/206 patients) in the group receiving fluconazole 300 mg repeated at 2 weeks were cured. Both groups receiving 300 mg per dose had a statistically significant higher cure rate than the group receiving 150 mg weekly.

There was no statistically significant difference between the groups receiving 300 mg per dose.

Montero-Gei et al. evaluated fluconazole 450 mg once (30 patients) versus two doses of fluconazole 300 mg given 1 week apart (30 patients) versus itraconazole 200 mg daily for 7 days (30 patients) in an open-label, randomized comparative trial.⁶ Patients were assessed by clinical examination and skin scrapings at 30 and 60 days after initiating therapy. At day 30, 60% of patients in the 1-dose fluconazole group were clinically cured versus 77% in the 2-dose fluconazole group—this was not statistically significant. However, 70% of patients in the 1-dose fluconazole group were mycologically cured versus 97% in the 2-dose fluconazole group—this was statistically significant ($p<0.012$, Fishers exact test). There appeared to be a trend for increased cure at 60 days in the 2-dose fluconazole group: the 1-dose fluconazole group had a 52% clinical cure and 55% mycologic cure at 60 days versus 70% clinical cure and 77% mycologic cure in the 2-dose fluconazole group. The differences at day 60, however, were not statistically significant.

CONCLUSION

Fluconazole is effective when dosed weekly. Dosing at 300 mg weekly for 4 weeks or single dose fluconazole 300 mg repeated in 2 weeks are more effective than fluconazole 150 mg weekly for 4 weeks. In addition, it appears multiple smaller doses (i.e., two or more 300 mg doses) of fluconazole may be more effective than a single large dose of fluconazole (i.e., 450 mg once). Hence, the optimal regimen for fluconazole appears to be a single 300 mg dose repeated two to four times, with each dose administered 1 to 2 weeks apart.

What We Know

- Oral azole antifungals (ketoconazole, itraconazole, and fluconazole) are highly effective against tinea versicolor.
- Selenium sulfide 2.5%, terbinafine 1%, and multiple azole antifungal agents are highly effective against tinea versicolor.
- Monthly oral azole antifungals reduce recurrences of tinea versicolor.
- Ketoconazole is highly effective in dosing regimens ranging from 400 mg once to 200 mg daily for one to several weeks.
- Itraconazole is highly effective at 1-gram cumulative dose, but lower cumulative doses appear to be just as effective.
- Fluconazole appears to be most effective as a single 300 mg dose, given 2 to 4 times at weekly intervals.

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Treatment of Cutaneous Leishmaniasis

28

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BACKGROUND

Leishmania genus is an obligate intracellular protozoan causing leishmaniasis in humans and other mammals and is related to trypanosomes. Its transmission takes place via bites of sandflies as vectors of the disease.^{1,2} The parasite has two forms in its life cycle called amastigote and promastigote. The amastigote is the non-flagellated form and the promastigote has flagellates. These forms convert into one another based on the parasite life cycle. The female sandfly takes the amastigotes from mammals' bodies. The amastigotes convert into the promastigotes in the midgut of sandfly. When sandflies feed once again, the promastigotes will be transferred into the host skin, which they bite. It has been reported that as low as 100 parasites can generate the number of promastigotes required for the development of acute cutaneous leishmaniasis (CL), and numbers less than that may produce a silent form of the disease which could generate a protective immune response in some infected individuals.^{2,3}

ETIOLOGY AND PATHOGENESIS

More than 20 species of *Leishmania* are human pathogens. Well-known species causing Old World CL (OWCL) are *L. major*, *L. tropica*, *L. aethiopica*, *L. donovani*, and *L. infantum*. The reservoirs for these *Leishmania* species are small rodents, humans, rock hyrax, human and canine family, respectively. Several species of the genus *Phlebotomus* are vectors involved in transmission of Old World parasites. *L. braziliensis*, *L. guyanensis*, *L. panamensis*, *L. mexicana*, *L. venezuelensis*, *L. amazonensis*, *L. chagasi*, and *L. peruviana* are the species causing New World CL (NWCL). The vectors of this group of parasites belong to the genus *Lutzomia*. Common reservoirs for causative agents of NWCL are: forest rodents, foxes, sloths, and dogs.^{1,4,5}

Phagocytic cells of monocyte lineage and dendritic cells engulf the parasites and a parasitophorous vacuole will be formed and after a short time of hours the promastigotes convert into amastigotes and start dividing within phagocytes.²

When the *Leishmania* promastigotes enter the host, they manage to evade hostile environment and innate and adaptive immune responses. C3b complement protein is involved

in opsonization of the parasites. Special surface glycoprotein of parasite called gp63 attaches to C3b and form into iC3b, which is an essential step for the parasite. Opsonization and engulfment by phagocytic cells assist parasites to survive. Upon internalization of the parasites, fusion of phagosome with lysosome occurs, *Leishmania* amastigotes survive and multiply within the phagolysosomes by various mechanisms. One of these mechanisms is protection by acid phosphatases, which prevents killing of *Leishmania* by oxidative burst. This mechanism is based on a proton pump, which maintains the intracellular pH close to normal. This will consequently inactivate macrophage acidic enzymes and inhibition of lysoso-mal enzymes by lipophosphoglycan (LPG) molecules.⁶ Multiplication of the amastigotes results in macrophage rupture and release of the amastigotes, which will infect other cells.^{7,8}

Clinical manifestations of *Leishmania* infection depends upon *Leishmania* species and host genetic background, which generate immune responses. The outcome of *L. major* infection in murine model depends upon the type of immune response generated. Most strains of mice are resistant to *L. major* infection and develop a lesion similar to human CL, which heals spontaneously. Recovered mice are resistant to further infection and generate a Th1 immune response with high level of IFN- γ and low level of IL-4. On the other hand, *L. major* infection in susceptible BALB/c mice induces a progressive and eventually fatal disease with generation of Th2 response with high level of IL-4 and low level of IFN- γ .⁹

Leishmania infection induces both humoral and cellular immune responses, protection depends on generation of cellular immune response, and antibody level is very low in CL.

EPIDEMIOLOGY AND BURDEN OF DISEASE

Leishmaniasis is a widespread disease, which occurs in tropical and subtropical regions all around the world except Australia continent.¹⁰ From the 1.5-2 million annual worldwide new cases of leishmaniasis, 1-1.5 million cases are CL. CL is the most common form of leishmaniasis.¹¹ In CL, the lesion(s) is(are) confined to the skin usually on the

exposed parts of the body like arms, legs and face.^{12,13} CL is endemic in more than 70 countries and in some of them, an increase in the number of diagnosed cases over the past few years has been reported, which can be explained by better diagnosis and case notification, inadequate control of vector or reservoir, increased CL detection accompanied with opportunistic infections such as HIV/AIDS, and the emergence of antileishmanial drug resistance.^{10,14} Ninety percent of CL occurs in Iran, Afghanistan, Algeria, Brazil, Peru, Saudi Arabia, and Sudan.^{15,16} CL is increasingly seen in immigrants, military personnel, humanitarian aid workers, tourists and travelers who travel to areas where leishmaniasis is endemic.¹² CL emergence in Europe as a result of climate and environmental changes has been reviewed.¹⁷

CLINICAL FEATURES

Although different clinical classifications have been suggested for CL, it may be simply categorized to three main groups: localized, diffuse, and mucocutaneous. While the first two forms can occur in either OWCL or NWCL, the latter is more frequently associated with NWCL. Another form of CL which is known as leishmaniasis recidivans also exists.^{18,19}

LOCAL CUTANEOUS LEISHMANIASIS (LCL)

OWCL

Based on clinical appearance of the lesion(s), OWCL is commonly classified to dry and wet forms. The dry form, known as the anthroponotic CL (ACL) (Figure 28-1), urban, or late ulcerative form is caused by *L. tropica*, whereas the wet form (Figure 28-2), which is synonymous to zoonotic CL (ZCL), rural or early ulcerative form is caused by *L. major*.²⁰ The sandfly-mediated transmission



FIGURE 28-1 ACL lesion caused by *L. tropica* on the nose of a young girl in a CL endemic area in Iran. An erythematous plaque with erosions and adherent crusts are typical for ACL lesions also known as dry type CL.



FIGURE 28-2 ZCL caused by *L. major* on the dorsal surface of the left foot of a young Iranian man in a CL endemic area in Iran. The ulcerated plaque with a violaceous border and moderate exudate is typical clinical presentation of a well-developed large ZCL lesion.

of parasites is from animals to humans in ZCL and from human to human in ACL. In most cases of ZCL, the lesion usually heals spontaneously in less than one year, but most cases of ACL undergo spontaneous healing after 6-15 months with significant scars. ACL and ZCL may rarely coexist in the same patient.¹

NWCL

New World CL most commonly appears as LCL. In this form, there are one or multiple ulcers.^{21,22} The first lesion is a papule or pimple, which appears at the parasite inoculation site. Like in OWCL, this lesion grows and converts into an ulcer, which is covered by dried exudates. The ulceration may not happen and papules turn into nodules instead.¹⁷ Healing usually occurs spontaneously. Lesions caused by *L. mexicana* usually heal spontaneously in months; however, in cases of *L. brasiliensis*, the healing takes much longer.²³ Spontaneous healing of the lesions is usually associated with scar formation.

DIFFUSE CUTANEOUS LEISHMANIASIS (DCL)

Diffuse cutaneous leishmaniasis is a form of CL, which manifests with multiple lesions in at least two non-contiguous areas of the body. The dissemination should be distinguished from multiple inoculations. The lesions are non-ulcerative cutaneous nodules. Mucosal lesions inmate appear in less than 1/3 of patients.²⁴

MUCOCUTANEOUS LEISHMANIASIS (MCL)

There is a small risk that CL evolves into mucocutaneous leishmaniasis (MCL), especially in certain parts of America where some *Leishmania* species, which are able to cause



FIGURE 28-3 Amputation of nose, upper and lower lips caused by MCL in a Bolivian patient (Courtesy of Dr. Philippe Desjeaux).

mucosal lesions (Figure 28-3) exist.²² In some cases, the skin and mucosal lesions exist simultaneously, however, in Amazonian Brazil and when the causative agent is *L. braziliensis*, mucosal involvement is the result of an untreated old skin lesion in approximately 60% of cases.²¹

LEISHMANIASIS RECIDIVANS (LR)

This rare form of CL, which is also called lupoid leishmaniasis or leishmaniasis recidiva cutis, occurs in 3-10% of OWCL caused by *L. tropica* and is characterized by slowly progressive persistent lupoid papules or nodules which are recrudescent and occur in or around healed lesions (Figure 28-4). LR lesions may be persistent for 2-8 years and some reports have described seasonal variations in lesions. A great majority of lesions occur on the face but they can also occur on other parts of the body. LR has been reported as a rare type of NWCL with the same clinical presentation of LR in OWCL. *L. amazonensis*, *L. braziliensis* and *L. panamensis* have been reported as the causative agents of the New World LR.^{1,25,26}

DIFFERENTIAL DIAGNOSIS

Differential diagnoses of CL include bacterial infections such as furuncles, methicillin-resistant *Staphylococcus aureus* infections, ecthyma, and anthrax; mycobacterial infections including cutaneous tuberculosis in particular lupus vulgaris, leprosy, *Mycobacterium marinum* or other atypical mycobacteria; spirochetal diseases such as syphilis and yaws; fungal infections like sporotrichosis, paracoccidioidomycosis, histoplasmosis and blastomycosis. CL may mimic clinical features of both granulomatous inflammatory skin diseases like sarcoidosis and non-granulomatous inflammatory skin diseases like psoriasis and eczema. Skin cancers including squamous cell carcinoma, basal cell carcinoma, and malignant melanoma may also resemble CL lesions. Other differential diagnoses are



FIGURE 28-4 Leishmaniasis recidivans caused by *L. tropica*. Flesh-colored papules surrounding an old scar caused by ACL on the right cheek of a young Iranian man.

pyoderma gangrenosum, insect bite and hyperkeratotic lesions such as warts.^{22,23,26,27}

DIAGNOSIS

The history of traveling to endemic areas is an important factor in the diagnosis of leishmaniasis in countries where the disease is not endemic.²⁴

A direct smear from the periphery of an active lesion is one of the most commonly performed diagnostic methods. Detection of parasites inside macrophages is not always easy; macrophages and amastigotes inside them have diameters of 20-30 and 2-5 micrometers, respectively. The parasites inside macrophages are called Leishman, Donovan or Leishman-Donovan bodies. Leishman-Donovan bodies have a plasma membrane, a large basophilic nucleus, and a small, rod-shaped kinetoplastid extranuclear DNA from the flagellum base. The Giemsa stain is the method of choice for smears obtained from patients since using this technique, the flagellum will become bright red.²⁶ Culture on Nicolle-Novy-MacNeal (NNN) culture medium may increase the chance for detection of *Leishmania*. Histopathology may also be helpful. Recently, polymerase chain reaction (PCR) has been shown as an accurate test for diagnosis of CL through detection of *Leishmania* DNA.¹³

TREATMENT

Five therapeutic systematic reviews have been published for various forms of CL in 2007 and 2008²⁸⁻³². Although because of the heterogeneity of the primary studies, the level of evidence of these systematic reviews may not be as high as the level of evidence provided by the systematic reviews of homogenous randomized-controlled trials (RCTs), the authors believe that they are the highest available evidence on the treatment of CL (Table 28-1).

TABLE 28-1—Characteristics of Published Systematic Reviews on Treatment of CL/MCL Up to the Beginning of May 2010

Study	Searched resources and time period	Number of included studies (total number of patients)	Inclusion criteria	Exclusion criteria
Gonzalez et al., 2009²⁹ (NWCL)	Cochrane Skin Group Specialized Register—January 2009, Cochrane Central Register of Controlled Trials, (CENTRAL) issue 1–2009, MEDLINE (OVID)—2003 to January 2009, EMBASE (OVID)—2005 to January 2009, CINAHL—1982–May 2007, LILACS from its inception to January 2009, American College of Physicians (ACP) journal club—1991 to May 2007, ongoing trials, references of published studies, unpublished studies Adverse effects – MEDLINE (Ovid) – 1950–2007	38 (2728)	RCTs assessing the treatment of American CL or MCL Immunocompetent people having clinical presentation of American CL or MCL confirmed by proper diagnostic methods	Trials which were not clearly a RCT on American CL or MCL
Gonzalez et al., 2008³⁰ (OWCL)	Cochrane Skin Group Specialized Register—April 2008, MEDLINE (OVID) and MEDLINE(R) In-Process—2003 to April 2008, EMBASE (OVID)—2005 to April 2008, CINAHL—1982 to August 29, 2007; LILACS –from inception to April 2008, American College of Physicians (ACP) journal club—1991 to May 2007, ongoing trials, references of published studies, unpublished studies Adverse effects –MEDLINE (Ovid)–1950–2007	49 (5559)	RCTs Immunocompetent patients having OWCL whose clinical diagnoses were confirmed by one of these methods: smear, histology, culture or polymerase chain reaction	Leishmaniasis forms other than MCL MCL cases outside Latin America
Tuon et al., 2008³¹ (NWCL)	MEDLINE, LILACS, EMBASE, Web of Science—January 1966 to August 2006, Cochrane Library to 2006, bibliographic references, from the included studies, reference sections of primary studies, narrative reviews, and systematic reviews	54 (2969)	RCTs Giving data which enables comparison between cure and failure Providing information about internal and external validity Demographic data on population under study such as location of the patients and common species At least 5 patients in case series of treatments	Papers on MCL treatment from Latin America Giving data which enables comparison between cure and failure Providing information about internal and external validity Demographic data on population under study At least 5 patients in therapeutic case series
Amato et al., 2007³² (NWMCL)	MEDLINE—1966 to January 2007, LILACS - 1982 to January 2007, EMBASE—1966 to January 2006, Web of Science—1965 to January 2007, Cochrane Library to 2006, bibliographical references, from the included studies, reference sections of primary studies, narrative reviews, and systematic reviews	22 (635)	Papers on MCL treatment from Latin America Giving data which enables comparison between cure and failure Providing information about internal and external validity Demographic data on population under study At least 5 patients in therapeutic case series	Cases of patients who traveled tropical areas
Khatami et al., 2007³³ (OWCL)	Cochrane Central, Register of Controlled Trials - 3rd quarter 2006, Ovid, MEDLINE—1966 to July 2006, EMBASE—1980 to July 2006, Early online and other electronic, formats of article, manual search on all available issues of medical journals published in Iran up to June 2006, references of relevant articles and reviews, bibliographies of retrieved publications	50 (5515)	RCTs Therapeutic trials Trials in areas of OWCL endemicity or the study stated that patient had OWCL Trials on acute OWCL	Trials on vaccines and any preventive measure

NWCL, new world cutaneous leishmaniasis; RCT, randomized-controlled trial; MCL, mucocutaneous leishmaniasis (MCL); OWCL, old world cutaneous leishmaniasis.

Randomized-controlled trials investigating systemic and local therapeutic interventions for OWCL have been demonstrated in Tables 28-2 and 28-3, and those trials, which are concerned on local and systemic treatments for NWCL, are presented in Tables 28-4 and 28-5, respectively. Tables 28-6 and Table 28-7 have demonstrated systemic and topical studies on treatment of MCL, respectively (Tables 28-2 to 28-7.)

TREATMENT OF OWCL

A wide array of RCTs on therapeutic interventions have been included, critically appraised, and summarized in the systematic reviews of Gonzalez et al. and Khatami et al.^{30,33} The quality of conduct and report of most of those RCTs were low, so the validity of their findings was questionable. In addition, because of heterogeneity of the included studies, comparing different studies was not possible in many instances, which made the resulted evidence less robust in terms of strength of evidence.^{30,33} Also, it worth to mention that studies on some of the treatment modalities not included in these reviews or in the analysis, could have been proved to be potentially beneficial if they had been designed and/or performed appropriately.

In the following lines, some facts are briefly pointed out that healthcare professionals should pay attention to while thinking of interpretation of the results of the above-mentioned systematic reviews and choosing a medication to treat patients are briefly pointed out:

- The information about the outcomes assessed is not provided completely in all studies and the outcomes are not accurately addressed in all of them.
- Only about 35% of studies reported randomization and only 14% of studies properly reported allocation concealment methods.
- The degree of functional and esthetic impairment as well as scar prevention, and quality of life has not been investigated in the studies.
- There is a lack of good quality evidence on treatment modalities such as, amphotericin B, healing promoting therapies and alternative therapy.
- There are only a few high-quality studies amongst the ones investigated. As Gonzalez et al. and Khatami et al. have only ranked three and five studies, respectively, as high-quality studies in terms of randomization, allocation concealment, blinding and intention-to-treat; two were on *L. major* infections and one was on *L. tropica*-infected patients.^{30,33}
- There is still no ideal treatment profile of one drug able to treat different species without serious adverse effect.
- Majority of studies reported their primary outcome results at the end of treatment or less than 3 months after the end of the treatment and did not consider/report cure rates around or after 3 months.

- A few studies reported the cure rates as lesion-based and majority reported it as patient-based.^{30,33}

The treatments will be categorized in four major groups including pentavalent antimonials including meglumine antimoniate and sodium stibogluconate, paromomycin, azole agents, and miscellaneous treatments.

PENTAVALENT ANTIMONIALS

The pre-assumption that different regimens of antimonials are more effective than placebo in treatment of OWCL lesions, could only be proved with properly designed and performed RCTs comparing them in terms of efficacy and adverse effects; the evidence which is currently lacking. Having said that, it should be mentioned that for decades, these drugs have been the first-line agents for the treatment of leishmaniasis.³⁴ To the best of the knowledge of the authors and up to the date of writing, this chapter there is no placebo-controlled RCT, which has properly assessed the effectiveness of pentavalent antimonials in the treatment of OWCL.

The intraleisional administration of sodium stibogluconate has been found to be more effective than its intramuscular injections.³⁵ Other studied regimens or routes of administration of antimonials have not been reported to be significantly different from their comparator.^{36,37}

Paromomycin

Twenty-eight days of topical 15% paromomycin + 12% methylbenzethonium chloride twice daily has been found to be significantly more efficient than placebo.³⁸ In a recent meta-analysis, it has been reported that paromomycin is only effective when combined with methylbenzethonium chloride. Paromomycin efficacy was reported not to be significantly different from intraleisional antimonials.³⁹

Azoles

Oral fluconazole with the dosage of 200 mg/day for 6 weeks is found to be better than placebo for *L. major* infections.⁴⁰ When the causative agent is *L. major*, oral itraconazole with the dosage of 200 mg once daily for 8 weeks has been shown to be marginally more effective than placebo.⁴¹ However, when the causative agent was *L. tropica*, oral itraconazole at 200 mg/day for 6 weeks provides significantly higher cure rates in comparison to the placebo.⁴² Other regimens of azole agents were not therapeutically more effective than their respective control interventions.⁴³⁻⁴⁸

MISCELLANEOUS

Four weeks of photodynamic therapy (PDT) have been reported to be more effective in treatment of the OWCL

TABLE 28-2—RCTs of Local and Topical Treatments for OWCL Based on the Khatami et al. and Gonzalez et al. Systematic Reviews^{30,33}

Study (Country)	Sample size (experimental group(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome	ARR (95% CI)*
Sadeghian et al., 2007 (Iran)	117 (57, 60)	Controlled localized heating with an radiofrequency (RF) heat generator (4 MHz, maximum output 90 W) to a surface temperature of 50°C for 30 seconds	IL MA 0.1-4 mL	180	Cure [†]	RR (95% CI): 0.72 (0.50-1.04) PB: 1.46 (1.18-1.80) LB: 1.42 (1.10-1.84)
Nilforoushzadeh et al., 2007 (Iran)	100 (50, 50)	Topical honey soaked gauze bid + IL MA IL 5% sodium chloride; 0.5-1 mL	IL MA	120	Cure [†] at 2.5-3 months post-treatment	RR (95% CI): 1.63 (1.11-2.39)
Sadeghian et al., 2006 (Iran)	72 (36, 36)	PDT for 4 weeks/weekly Topical paromomycin 15% bid for 28 days	Placebo	180	Cure [†]	RR (95% CI): 81.4 (60.6-90.1) 27.9 (6.9-45.9)
Asilian & Davami, 2006 (Iran)	60 (20, 20, 20)			90	No induration + no inflammation + complete re-epithelialization + PC	
Salmanpour et al., 2006 (Iran)	60 (20, 20, 20)	(1) Cryotherapy + ILMA weekly for a total of 6-8 times (2) IL MA alone weekly for a total of 6-8 times	Cryotherapy weekly for a total of 6-8 times	NR	Cure [†]	CR (%): 89 (Experiment-1 and Control), CR (%): 67.8 (Experiment-2 and Control)
Reithinger et al., 2005 (Afghanistan)	401 (138, 146, 117)	Single session of thermotherapy	(1) IL SSG injections every 5-7 days (2) IM SSG 20 mg/kg/day for 21 days	121	Complete re-epithelialization of lesions without any sign of induration	-6.4 (-5.2-17.7) 35.5 (24.0-45.6)
Crawford et al., 2005 (Iran)	99 (35, 35, 29)	IL MA weekly + topical 5% imiquimod cream 3 times/wk for 40 day	(1) IL MA weekly for 40 days (2) Topical 5% imiquimod cream 3 times/wk for 40 days	40	Decrease in size of erythema, induration, and ulceration	-14.3 (-34.0-7.1) -11.6 (-32.8-10.1)
Firooz et al., 2005 (Iran)	72 (36, 36)	IL ZnSO ₄ solution weekly up to complete healing or for 6 wks	IL MA weekly up to complete healing or for 6 wks	49	Complete re-epithelialization lesions with marked reduction in induration with or without scarring	-32.1 (-45.8 to-17.5)
Sadeghian et al., 2005 (Iran)	72 (36, 36)	IL 7% NaCl solution weekly injections for 42 days	IL MA weekly injections for 42 days	42	Complete disappearance of induration+re- epithelialization	-8.3 (-28.2 -12.4)

Iraji and Sadeghinia, 2005 (Iran)	65 (30, 35)	Topical paromomycin 15% bid for 30 days	Placebo	60	At least 75% reduction in lesion size and reduction in lesion induration+amastigote-free smears	Day 30: -0.5 (-18.6-18.7) Day 60: -3.3 (-21.8-16.3)
Shazad et al., 2005 (Iran)	60 (30, 30)	Topical paromomycin 15% bid for 20 days	IL MA qod up to complete healing or 20 days	42	Complete re-epithelialization of all lesions at 1 week post-treatment	6.7 (-16.9-29.3)
Asilian et al., 2004 (Iran)	400 (100, 200, 100)	IL MA fortnightly for 4 wks + cryotherapy to complete healing or a maximum of 6 wks	(1) Cryotherapy to Complete healing or a maximum of 6 wks (2) ILMA fortnightly for 6 wks or complete healing	180	Complete re-epithelialization and disappearance signs of inflammation+PC	LB = 41.4 (31.8-49.6) LB = 28.3 (17.7-37.5)
Niforoushzadeh et al., 2004 (Iran)	210 (105, 105)	15% paromomycin+10% urea applied bid for 4 wks + Cryotherapy with liquid nitrogen repeated every two weeks till complete healing or for a maximum of three sessions + ILMA twice a week till complete healing or for a maximum of 6 wks	IL MA similar to experiment group	42	Complete re-epithelialization+disappearance of signs of inflammation	10.5 (-2.8-23.2)
Iraji et al., 2004 (Iran)	104 (56, 48)	IL ZnSO ₄ solution fortnightly up to complete healing or for 6 wks	IL MA fortnightly up to complete healing or for 6 wks	42	Total clearance of lesion + PC + marked size reduction ≥ 60% + PC	2.7 (-16.0-21.0)
Asilian et al., 2003 a (Iran)	233 (116, 117)	Topical paromomycin 15% bid for 4 wks	Topical 15% paromomycin bid for 2 wks + placebo for additional 2 wks	180	Parasitologic cure + clinical improvement or clinical improvement alone irrespective of PC	Day 29: 15.1 (2.8-26.8) Day 45: 13.4 (0.9-25.4) Day 105: 0.5 (-1.9-12.9)
Asilian et al., 2003 b (Iran)	180 (40, 40, 100)	(1) IL MA fortnightly for 6 wks or complete healing + cryotherapy to complete healing or maximum of 9 wks (2) IL SSG fortnightly for 6 wks or complete healing +cryotherapy to complete healing or maximum. of 6 wks	IL MA fortnightly for 6 wks or complete healing	180	Complete re-epithelialization and disappearance of inflammation size + PC	39.6 (27.6-48.5) 42.3 (30.7-50.8)
Faghhi and Tavakoli-kia, 2003 (Iran)	96 (48,48)	Topical paromomycin 15% bid for 3 months	IL MA weekly for 3 months or complete healing	365	re- epithelialization + return to normal skin texture in < 2 months + no residual scar + no relapse in FU period	-25.0 (-41.2 to -6.8)

(Continued)

TABLE 28-2—RCTs of Local and Topical Treatments for OWCL Based on the Khatami et al. and Gonzalez et al. Systematic Reviews^{30,33} (Continued)

Study (Country)	Sample size (experimental group(s), control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome	ARR (95% CI)*
Momeni et al., 2003 (Iran)	90 (45,45)	Topical ketoconazole bid for 21 days	Placebo	51	all lesions were healed + PC	Day 21: 1.5 (-15.7-18.2)
Nilforoushzadeh et al., 2003 (Iran)	80 (40, 40)	Topical TCA 50% 3 times every 2 wks	IL MA weekly up to complete healing or for 6 wks	90	Complete disappearance of induration + re-epithelialization	7.5 (-13.4-27.5)
Mapar et al., 2001 (Iran)	96 (52, 44)	Topical 10% opium in petrolatum bid for 2 wks	Placebo	56	Considerable (not exactly defined) reduction in size, induration, and inflammation of lesion + PC	-7.3 (-3.6-18.5)
Gholami et al., 2000 (Iran)	197 (96, 85)	Topical garlic 5% bid for 3 wks	Placebo	51	Complete healing + PC	-1.3 (-13.6-10.4)
Zerehsaz et al., 1999 (Iran)	171 (85, 86)	Topical Z-HE for 5 consecutive days + placebo	IM MA 15-20 mg/kg/d + placebo	42	Clinical improvement with complete healing + lesions re-epithelialization	47.4 (32.9-58.9)
Mujtaba et al., 1999, (Pakistan)	104 (49, 55)	IL MA injections weekly until complete cure or up to 8 wks	IL MA injections fortnightly until complete cure or up to 8 wks	60	Cure [†]	RR (95% CI): 1.07 (0.98-1.18)
Sharquie et al., 1997 (Iraq)	85 (76, 9)	(1) IL 2% ZnSO ₄ solution every 10-15 d up to 6 wks or complete healing (2) IL SSG every 10-15 days up to 6 wks or complete healing (3) IL 7% NaCl every 10-15 d up to 6 wks or complete healing	No treatment	45	Total clearance of lesions + PC + size reduction = 60% + PC	94.7 (79.6-98.5) 85.0 (68.2-92.9) 88.6 (71.4-95.5)
Asilian et al., 1995 (Iran)	251 (125,126)	Topical 15% paromomycin bid for 2 wks	Placebo	105	Complete re-epithelialization on either day 45 or day 105	Day 45: 1.1 (-10.9-13.1) Day 105: 1.3 (10.5-13.4)
Larbi et al., 1995 (KSA)	151 (89, 62)	Topical 1% clotrimazole for 30 days	Topical 2% miconazole for 30 days	30	Completely healed lesions + PC reduction in infiltration, erythema and size of the lesion	40.3 (24.6-53.0)
Ben Salah et al., 1995 (Tunisia)	115 (57, 58)	Topical 15% paromomycin bid for 2 wks	Placebo	105	Parasitologic cure + any degree of re-epithelialization + at least 50% size reduction at day 45	8.9 (-3.1-21.2)
el-Safi et al., 1992 (Sudan)	40 (62 lesions) (20 [32 lesions], 20 [30 lesions])	Topical 15% paromomycin bid for 10 days	Placebo	30	No clear defining criteria for response and non-response	-20.0 (-44.5-8.2)

Lynen and Van Damme, 1992 (Sudan)	66 (33, 33)	Topical 1.05 g of diminazene aceturate in 2.36 g of granule dissolved in 12.5 mL of distilled water daily except Fridays for 50 days	Topical 15% cetrinimide + 1.5% chlorhexidine in 2% solution daily except Fridays for 50 days	80	Complete closure and covering of lesions with scar tissue, w/o possibility to evoke secretions on pressure + sustaining apparent cure for >2 wk	21.2 (0.8- 40.0)
el-On et al., 1992 (Israel)	39 (30, 32, 11, 9) (Cross over study)	Topical 15% paromomycin 12% MBCL bid for 20 days	Placebo	90	Parasitologic cure + complete healing of lesion	No ARR reported to maintain the homogeneity
		Topical 15% paromomycin 12% MBCL bid for 10 days				
		Topical 15%paromomycin 5% MBCL bid for 20 days				
		Topical 15% paromomycin 5% MBCL bid for 10 days				
Harms et al., 1991 (Syria)	40 (20, 20)	IL recombinant IFN- γ 25 micrograms weekly for 5 consecutive wks	IL MA weekly for 5 consecutive wks	70	Smooth scar + undetectable number of parasites	LB = -73.6 (-84.5-[-54.5])
Trau et al., 1991 (Israel)	15 (3, 5, 7)	(1) Topical IFN- β 4-6 times/d for 4 wks (2) Topical IFN- β 4-6 times/d for 8 wks	(1) Placebo 4-6 times/d for 4 wks (2) Placebo 4-6 times/d for 8 wks	56	Decrease in lesion diameter of at least one fourth of original size	Day 28: -50.0 (-22.8-81.2) Day 56: 0.0 (-38.8-38.8)

*For some studies relative risk (RR) or cure rate (CR) has been reported.

[†]Gonzalez et al. defined cure when all inflammatory signs disappeared and complete healing through either scar formation or complete re-epithelialization occurred.³⁰ FUD, follow-up duration; ARR, absolute risk reduction; CI, confidence interval; IL, intrallesional; MA, meglumine antimoniate; RR, Risk ratio; PB, patient based; LB, lesion-based; bid, two times a day; NaCl, sodium chloride; PC, parasitological cure; PDT, photodynamic therapy; NR, not reported; CR, cure rate; bid, twice a day; wks, week(s); M, intramuscular; SSG, sodium stibogluconate; wk(s), week(s); ZnSO₄, zinc sulfate MBCL, methylbenzethonium chloride; TCA, trichloroacetic acid; Z-HE, Zerehsaz herbal extract; IFN- γ , interferon-gamma; IFN- β , interferon-beta.

TABLE 28-3—RCTs of Systemic Treatments for OWCL Based on the Khatami et al. and Gonzalez et al. Systematic Reviews^{30,33}

Study (Country)	Sample size (experimental, control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome	ARR (95% CI)
Mohebali et al., 2007 (Iran)	63 (32, 31)	Oral miltel fosine 2.5 mg/kg daily for 28 days	IM MA 20 mg/kg/d for 14 days	180	Cure*	RR (95% CI): 1.01 (0.79- 1.28)
Firooz et al., 2006 (Iran)	119 (59, 60)	IM MA 20 mg Sb ⁵⁺ /kg/d for 2 wks + 5% topical imiquimod cream qod for 4 wks	IM MA 20 mg Sb ⁵⁺ /kg/d for 2 wks + 5% topical imiquimod cream qod for 4 wks	140	≥75% reduction in lesion size compared with baseline at 8 wks	-4.3 (-21.4 to 13.37)
Sadeghian and Nilforoushzadeh, 2006 (Iran)	64 (32, 32)	IM MA 20 mg Sb ⁵⁺ /kg/d for 2 wks+oral pentoxifylline 400 mg 3 times/d for 20 days	IM MA 20 mg Sb ⁵⁺ /kg/d for 2 wks + placebo 3 times/d for 20 days	110	Flattening of the lesions + no induration + appearance of epidermal Creases	31.3 (8.0 -50.4)
Jaffar, 2006 (KSA, Bahrain)	62 (46, 16)	Rifampicin orally in a dose of 10 mg/kg/d	Placebo	90	Cure* at 3 months post-treatment	RR (95% CI) 2.43 (0.84-7.08)
Kochhar et al., 2006, (India)	50 (25, 25)	Rifampicin (1200 mg/day) in two divided doses+omeprazole 20 mg for 6 wks	Placebo	42	Cure*	CR (%): 64 (Experiment) CR (%):12 (Control)
Nassiri Kashani et al., 2005 (Iran)	200 (100,100)	Oral itraconazole 200 mg/d for 8 wks	Placebo	56	Complete re-epithelialization of all lesions reduction in size of lesion	5.7 (-9.6 to 20.7)
Nilforoushzadeh et al., 2005 (Iran)	150 (50, 50)	(1) IM MA 30 mg/kg/d 1 oral omeprazole 40 mg/d for 3 wks (2) IM MA 30 mg/kg/d 1 Placebo 40 mg/d for 3 wks	IM MA 60 mg/kg/d for 3 wks	90	Complete clinical cure + PC	-16.0 (-32.4-1.6) -8.0 (-24.2-8.8)
Dandashi, 2005 (Syria)	65 (46,19)	Fluconazole 200 mg/d for 6 wks	Placebo	NR	Cure*	CR (%):28.4 (Experimental) CR (%):9.8 (Control)
Famili et al., 2005 (Iran)	60 (31, 29)	Oral fluconazole 100 mg/d for 3 wks	IM MA 20 mg Sb ⁵⁺ /kg/d for 3 wks	42	Disappearance or 75% reduction of in lesion size + PC	-25.0 (-44.7 to -3.0)
Asilian et al., 2004 (Iran)	233 (110, 123)	CO ₂ laser	IM MA 50 mg/kg/d for 2-wk courses with a 2-wk rest (no treatment) period	90	Surface re-epithelialization, lesions flattening + PC	LB = 13.6 (4.4 -22.6)
Alrajhi et al., 2002, (Iran)	209 (106, 103)	Oral fluconazole 200 mg/d for 6 wks	Placebo	210	Cure*	Day 90: 38.1 (25.1-49.3)
Esfandiarpour and Alavi, 2002 (Iran)	150 (50, 50)	(1) Oral allopurinol 15 mg/kg/d for 3 wks (2) IM MA 30 mg/kg/d for 2 wks + oral allopurinol 20 mg/kg/d for 3 wks	IM MA 30 mg/kg/d for 2 wks	51	>80% reduction in lesion size inflammation and edema subsidence and lesion flattening size reduction by 50%	-6.0 (-22.8 -11.3) 24.0 (4.7-41.0)

Momeni et al., 2002 (Iran)	72 (36, 36)	IM MA 30 mg/kg/d+oral allopurinol 20 mg/kg/d	IM MA 60 mg/kg/d for 20 days	51	Healing of all lesions + PC	Day 21: 5.6 (-16.3-26.7) Day 51: -2.8 (-30.0-17.7)
Sharquie et al., 2001 (Iraq)	130 (115, 15)	(1) Oral ZnSO ₄ 2.5 mg/kg/d for 31.8 (+/-) 1.8 d (2) Oral ZnSO ₄ 5 mg/kg/d for 29.9 (+/-) 1.7 d (3) Oral ZnSO ₄ 10 mg/kg/d for 28.3 (+/-) 1.4d	No treatment	45	Total clearance of lesions + PC + size reduction ≥ 60% + PC	79.5 (54.2-89.2) 73.0 (47.1-84.6) 66.7 (41.0-94) For three experiment groups, respectively
Salmanpour et al., 2001 (Iran)	96 (32, 64)	Oral ketoconazole 600 mg/d for adults and 10 mg/kg/d for children for 30 days	IL MA biweekly for 6-8 wks	210	Complete re-epithelialization of lesions + little or no scarring at 6 wks	17.2 (1.2 to 35.3)
Mashhood et al., 2001 (Pakistan)	40 (20, 20)	IV SSG 20 mg /kg/day for 15 days	90	Cure*	CR: 85 (Experiment) CR: 70 (Control)	
Kochhar et al., 2000 (India)	50 (25, 25)	Oral rifampicin 600 mg bid for 4 wks	Placebo	18	Complete healing and Lesion disappearance on reversible hypopigmentation At lesion site	64.0 (39.0-79.2)
Alkhawaja et al., 1997 (KSA)	80 (40, 40)	IM MA 15 mg/kg/d daily on 6 days/ week up to 12 injections	IL MA 0.2 to 0.8 mL/lesion every other day over 30 days or till blanching of lesions	30	Cure*	5.1 (-10.3-20.1)
Ozgostasi and Baydar, 1997 (Turkey)	72 (32, 40)	Oral ketoconazole 400 mg/d and 200 mg/d for children <12 yr of age for 30 days	Topical paromomycin 15% bid for 15 days	30	Complete healing + lesion disappearance incomplete healing + lesion size reduction + parasitologic cure	-37.5 (-53.0 to -20.4)
Momeni et al., 1996, (Iran)	140 (70, 70)	Oral itraconazole 7 mg/kg/d for 3 wks	Placebo	51	Cure* + PC	Day 21: -1.4 (-13.1-10.3) Day: 12.9 (-3.5 to 28.3)
Droga et al., 1996 (India)	20 (10, 10)	Oral itraconazole (two 100 mg capsules) for 6 wks	Placebo	90	Cure*	RR (95% CI): 7.00 (1.04, 46.95)
Alsaleh et al., 1995, (Kuwait)	33 (15, 18)	Oral ketoconazole 800 mg/d for 6 wks	Oral ketoconazole 600 mg/d for 6 wks	180	>90% improvement (re-epithelialization, inflammation, size) + PC	-6.7 (-36.3 - 23.9)

(Continued)

TABLE 28-3—RCTs of Systemic Treatments for OWCL Based on the Khatami et al. and Gonzalez et al. Systematic Reviews^{30,33} (Continued)

Study (Country)	Sample size (experimental, control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome	ARR (95% CI)
Dogra, 1991 (India)	120 (60, 60)	Oral dapsone 100 mg every 12 hours for 6 wks	Placebo	45	Complete disappearance of induration/redness in nodular form or complete healing in ulcerative form + 3 consecutive NSs at 10-day intervals after completion of therapy, the first immediately after end of therapy	45.0 (27.9-58.5)
Al-Fouzan et al., 1991 (Kuwait)	24 (15, 9)	Oral itraconazole 100 mg bid for 6-8 wks	Placebo	105-140	>80% reduction of lesion size up to complete clearance	73.3 (34.2 - 89.1)
Dogra et al., 1990 (India)	20 (15, 5)	Oral single daily itraconazole, 4 mg/kg up to 200 mg/d for 6 wks	No treatment	90	Complete disappearance of induration or redness in nodular form Complete healing in ulcerative form+3 consecutive NSs at monthly intervals after therapy	66.7 (16.6 - 84.8)
Dogra et al., 1986 (India)	65 (50, 15)	Oral dapsone 2 mg/kg/d for 21 days	No treatment	201	Complete disappearance of induration or redness in nodular form or complete healing in ulcerative form + PC	80.0 (55.8-88.8)

*Gonzalez et al, defined cure when all inflammatory signs disappeared and complete healing through either scar formation or complete re-epithelialization occurred.³⁰ FUD, follow-up duration; ARR, absolute risk reduction; CI, confidence interval; IM, intramuscular; MA, meglumine antimoniate; wk(s), week(s); CR: cure rate; zinc sulfate; IL, intralesional; RR, risk ratio; qod, every other day; PC, parasitologic cure; IV, intravenous; SSG, sodium stibogluconate; LB, lesion-based; bid, twice a day; NS, negative smear.

TABLE 28-4—Topical Treatments for NWCL Based on Gonzalez et al. and Tuon et al. Systematic Reviews^{29,31}

Study (Country)	Sample size (experiment(s), control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome*	CR (%) or RR (95% CI)
Lobo et al., 2006 (Brazil)	37 (17, 20)	Single session of heat therapy	IV MA 20 mg/kg/d for 20 consecutive days	28	Cure	59.0 (Experiment) 10.0 (Control)
Soto et al., 2002 (Colombia)	45 (33, 12)	Topical WR279396 with 0.0005 mL/mm ² bid for 20 days	Placebo	200	Cure (70 days)	51.5 (Experiment) 47.1 (Control)
Arana et al., 2001 (Guatemala)	76 (38, 38)	Topical 15% paromomycin + 12% MBCL bid for 20 days	Topical placebo (white soft paraffin) ointment	365	Cure	2.38 (1.50, 3.80)
Neva et al., 1997 (Honduras)	53 (23, 30)	Topical 15% paromomycin + 10% urea tds for 4 weeks	Placebo	105	Cure (75 days)	4.3 (Experiment) 3.3 (Control)

*Based on Gonzalez et al, "Cure" has been defined as when all inflammatory signs have disappeared (either skin edema or hardening, or both), and that scarring or epithelialization has occurred in ulcerative lesions.²⁹ The figures in the parenthesis indicate the time point at which cure is defined in the primary study. FUD, follow-up duration; CR, cure rate; RR, relative risk; CI, confidence interval; qod, every other day; IV, intravenous; MA, meglumine antimoniate; bid, twice a day; MBCL, methylbenzethonium chloride; tds, three times a day.

lesions compared to placebo when the causative agent was *L. major*. It was also more effective than topical application of 15% paromomycin+12% methylbenzethonium chloride cream twice daily for 28 days.⁴⁹

Oral pentoxifylline has been found to be an appropriate adjuvant to intramuscular meglumine antimoniate therapy.⁵⁰ When the infection is caused by *L. tropica*, the heat therapy provides significantly higher cure rates compared to the intramuscular sodium stibogluconate but not to intralesional sodium stibogluconate.³⁵

Compared to intramuscular meglumine antimoniate, once weekly heat therapy for 4 weeks has been reported to result in significantly higher cure rates.⁵¹

Other treatment options including oral miltefosine,⁵² topical 5% imiquimod,^{53,54} and usage of honey as adjuvant to intralesional meglumine antimoniate injections,⁵⁵ have not been found to provide clinically or statistically significant results. RCTs conducted on oral allopurinol alone or combined with antimonials,^{56,57} and topical antifungal medications,^{58,59} did not show significant advantage of the experiments in comparison with controls too. Results of RCTs for oral and intralesional zinc sulphate were conflicting,^{60–63} as well as those of oral rifampicin.^{64,65} However, adding oral omeprazole to oral rifampicin has been reported to be significantly more effective than placebo in the treatment of OWCL caused by *L. tropica*.⁶⁶

Oral dapsone,^{67,68} combined cryotherapy-intralesional injection of pentavalent antimonials as well as one CO₂ laser RCT^{69–72} showed significant beneficial effects. This is the same for RCTs on trichloroacetic acid (TCA), Zerehsaz herbal extract (Z-HE) and healing promoting

measures.^{73–75} Results of RCTs on garlic cream, intralesional hypertonic saline solution and intralesional INF-γ were generally poor.^{76–78}

TREATMENT OF NWCL

Before beginning to discuss treatment options for NWCL and/or MCL, the authors would like to mention some points about Amato et al. systematic review.³² Considering the fact that almost all of the included studies in the aforementioned review were nonrandomized and/or uncontrolled, only two studies from their reviews are provided in Table 28-6. Using the critical appraisal skills programme (CASP) tool⁷⁹ for systematic reviews screening questions, this review did not have the proper design to be categorized as a systematic review of RCTs on treatment of ML. Hence, this review was excluded from the major resources used to write this section. The authors imagine that the following points have to be reminded with regard to Amato et al. review³²: (1) all except two studies were nonrandomized; (2) no study was blinded; (3) only half of the studies had inclusion criteria; (4) only 3 studies had exclusion criteria; (5) only 3 studies have been ranked by the authors as high quality studies; and (6) often because of the insufficient number of participants, no statistical analysis has been performed.

The general agreement based on the reviews of Gonzalez et al.²⁹ Tuon et al.³¹ and Amato et al.³² is that several factors such as treatment cost, adverse effects, local experience of clinicians, and availability of the medications should be considered in developing countries. These should be

TABLE 28-5—Systemic Treatments for NWCI Based on Gonzalez et al. and Tuon et al. Systematic Reviews^{29,31}

Study (Country)	Sample size (experimental, control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome [†]	RR (95% CI) or CR (%)
Arevalo et al., 2007 (Peru)*	20 (6, 7, 7)	(1) Topical imiquimod 7.5 % cream qod for 20 days (2) Topical imiquimod 7.5 % cream qod for 20 days + IV MA 20 mg/kg/d for 20 days	IV MA 20 mg/kg/d for 20 days	90	Cure	0.13 (0.01-1.97) (Experiment-1 and Control) 1.67 (0.88-3.15) (Experiment-2 and Control)
Andersen et al., 2005 (Peru)	80 (40, 40)	IV pentamidine isethionate 2 mg/kg on alternate days for 7 doses	IV MA 20 mg (Sb)/kg/day for 20 days	180	Cure	0.45 (0.29-0.71)
Miranda-Verastegui et al., 2005 (Peru)*	40 (20, 20)	Topical imiquimod cream 5% qod for 20 days + IM MA in children or by slow IV MA (>15 minutes) in older subjects for 20 days	Topical placebo cream qod for 20 days + IM MA same as in experiment group	360	Cure	0.87 (0.58-1.30)
Armijos et al., 2004 (Ecuador)	120 (40, 40, 40)	(1) Topical paromomycin 15% + 12% MBCL ointment bid for 30 days (2) Topical paromomycin 15% + 10% urea bid for 30 days	IM MA 20 mg of Sb/kg/day for 10 days	360	Cure	CR: 47.5 (Experiment-1) CR: 47.5 (Experiment-2) CR: 70 (Control)
Soto et al., 2004 a (Bolivia and Colombia)	114 (48, 16, 50)	IM SSG 20 mg/Kg/d for 20 days IM SSG (Pentostam [®])20 mg/kg/d for 20 days	IM MA 20 mg/kg/d for 20 days	180	Cure	1.07 (0.88-1.30) (Experiment-1 and Control) 1.11 (0.82-1.51) (Experiment-1 and Experiment-2)
Soto et al., 2004 b (Colombia and Guatemala)	133 (49, 24, 50)	Oral miltefosine 50 mg for 28 days IM SSG 20 mg/Kg/d	Placebo	180	Cure	2.18 (1.28-3.71) (Colombia) 2.50 (0.99-6.33) (Guatemala)
Santos et al., 2004 (Brazil)*	22 (11, 11)	GM-CSF (final concentration of 10 µg/mL) 3 times/wk for 3 wks (a total of 9 GM-CSF applications)+ IV MA 20 mg/kg/d for 20 days	IV MA 20 mg/kg/d for 20 days	365	Cure (40 days)	CR: 91 (Experiment) CR: 45.5 (Control)
Machado-Pinto et al., 2002 (Brazil)	102 (51, 51)	Subcutaneous injection of <i>L. amazonensis</i> vaccine (0.5 mL) daily + IM MA (8.5 mg/kg) for 10 days followed by 10 days of rest	Subcutaneous injection of placebo (0.5 mL) daily + IM MA (8.5 mg/kg) for 10 days followed by 10 days of rest	365	Cure	CR: 92.15 CR: 7.84
Palacios et al., 2001 (Colombia)	136 (68, 68)	IM MA 20 mg/kg/d (no upper limit on the daily dose) qod during 10 days	IM MA 20 mg/kg/d (no upper limit on the daily dose) qod during 20 days	365	Cure	1.17 (0.76-1.79)
Deps et al., 2000 (Brazil)	63 (32, 31)	IM MA 15 mg/kg/d for 20 days	IM SSG 15 mg/kg/d for 20 days	90	Cure	CR: 81 (Experiment) CR: 77 (Control)

Figueiredo et al., 1999 (Brazil)[†]	43 [24 (14 with ML and 10 with CL), 19 (7 with ML and 12 with CL)]	IV MA (14 mg/kg/d) alternated with placebo (in 2 series of 20 days having 15-days intervals in CL; IV MA (28 mg/kg/d) for 10 days and the other 10 d with placebo 3 series of 30 days having 15-days intervals in ML)	IV MA (28 mg/kg/d) for 10 days and the other 10 d with placebo (in 2 series of 20 days having 15-days intervals in CL; IV MA (28 mg/kg/d) for 10 days and the other 10 d with placebo 3 series of 30 days having 15-days intervals in ML)	730	Cure	CL: 1.50 (0.81-2.78) ML: 1.43 (0.53-3.86) CL+ML: 1.49 (0.88-2.54)
Almeida et al., 1999 (Brazil)	20 (10, 10)	GM-CSF received 2 local injections of 200 µg of hr-GM-CSF at entry and 1 week later + IV SSG at 20 mg/kg/d for 20 days	IV SSG (20 mg/kg daily for 20 days) + Saline (2 local injections of saline at entry and after 1 week)	180	Cure	CR: 70 (Experiment) CR: 10 (Control)
Soto et al., 1998 (Colombia)	150 (59, 30, 30, 32)	(1) Topical 15% paromomycin sulphate + 12% MBCL bid for 10 days + a 7-day short course of IV MA (2) Topical 15% paromomycin sulphate + 12% MBCL bid for 10 days + a 3-day short course of IV MA	(1) Topical placebo bid for 10 days + a 7-day short course of IV MA (2) IV MA for 20 days	365	Cure	1.08 (0.72-1.61) (Experiment-1 and Control -1) 2.88 (1.36-6.09) (Experiment-1 and Experiment-2) 0.38 (0.17-0.83) (Experiment-2 and Control-1) 0.69 (0.53-0.90) (Experiment-1 and Control-2) 0.24 (0.11-0.50) (Experiment-2 and Control-2)
Velez et al., 1997 (Colombia)	187 (60, 56, 66)	(1) Oral allopurinol 300 mg 3 (100-mg tablets) qid for 28 days (dosage: approximately, 5 mg/kg) (2) IM MA 20 mg/kg/d (no maximum daily dose) for 20 days	Oral placebo	365	Cure	1.06 (0.61-1.85) (Experiment-1 and Control) 2.74 (1.80-4.18) (Experiment-2 and Control) 0.39 (0.26-0.58) (Experiment-1 and Experiment-2)
Martinez et al., 1997 (Colombia)	100 (51, 49)	Oral allopurinol 20 mg/kg/d in 4 divided doses for 15 days + IV SSG 20 mg/kg/d for 15 days	IV SSG 20 mg/kg/day for 15 days	365	Cure	1.82 (1.23-2.70)
Neva et al., 1997 (Honduras)	53 (23, 30)	Topical 15% paromomycin + 10% urea	Placebo	105	Cure (75 days)	CR: 4.3 (Experiment) CR: 3.3 (Control)
D'Oliveira et al., 1997 (El Salvador)	34 (18, 16)	Oral allopurinol 20 mg/kg tds for 20 days	IV MA 10 mg/kg qd for 20 days	365	Cure (70 days)	CR: 0 (Experiment) CR: 50 (Control)

(Continued)

TABLE 28-5—Systemic Treatments for NWCL Based on Gonzalez et al. and Tuon et al. Systematic Reviews^{29,31} (Continued)

Study (Country)	Sample size (experimental group(s), control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome [†]	RR (95% CI) or CR (%)
Oliveira-Neto et al., 1997 (Brazil)	23 (12, 11)	IV MA 5 mg/kg/d	IV MA 20 mg/kg/d	2555	Cure	CR: 83 Experiment CR: 82 Control 1.22 (0.94-1.58)
Correia et al., 1996 (Brazil)	46 (15, 15, 16)	IM pentamidine isethionate 1.4 mg/kg/every 2 days for 8 applications MAminosidine sulfate 20 mg/kg/d for 20 days	IM MA 10 mg/kg/d for 20 days	365	Cure	0.23 (0.07-0.73) (Experiment-1 and Experiment-2) 0.20 (0.06-0.62) (Experiment-1 and Control) 0.87 (0.50-1.49) (Experiment-2 and Control)
Soto et al., 1994 (Colombia)	90 (30, 30, 30)	IM aminosidine sulfate 12 mg/kg/d (maximum daily dose: 850 mg) for 7 days IM aminosidine sulfate 12 mg/kg/d (maximum daily dose: 850 mg) for 14 days	IM aminosidine sulfate 18 mg/kg/d (maximum daily dose: 850 mg) for 14 days	365	Cure	1.15 (0.96-1.39) (Experiment-1 to (Control) 1.22 (0.99-1.50) (Experiment-2- Control) 0.95 (0.73-1.23) (Experiment-1 and Experiment-2)
Arana et al., 1994 (Guatemala)	66 (22, 22, 22)	(1) IV MA infusion over 15 minutes, 20 mg Sb/kg/d for 20 days (2) IV MA infusion over 15 min, 20 mg Sb/kg/d for 10 days + 10 days of a saline infusion	IV MA infusion over 15min, 20mg Sb/kg/d for 10 days + IFN- γ	365	Cure	CR: 59 (Experiment) CR: 88 (Control)
Hepburn et al., 1994 (Belize)	34 (17, 17)	IV aminosidine sulfate 14 mg/kg/d (maximum 1g/d)	IV SSG 20 mg/kg/day	180	Cure (45 days)	CR: 96 (Experiment-1) CR: 52(Experiment-2) CR: 20 (Control)
Navin et al., 1992 (Guatemala)	120 (40, 40, 40)	(1) Oral ketoconazole 600 mg/d for 28 days (2) IV SSG 20 mg of antimony/kg/d for 20 days	Placebo	365	Cure (60 days)	13.24 (0.83-210.87) 2.20 (1.34-3.60) 2.04 (1.25-3.34)
Martinez and Marr, 1992 (Colombia)	110 (25, 33, 35, 17)	(1) Oral allopurinol 20 mg/kg/d in 4 divided doses for 15 days (2) IV MA 20 mg/kg/d for 15 days (3) Oral allopurinol+ MA (same dosage)	No treatment	365	Cure	CR: 30 (Experiment-1) CR: 90 (Experiment-2) CR: 60 (Control)
Guderian et al., 1991 (Ecuador)	75 (30, 30, 15)	(1) Oral allopurinol ribonucleoside (1500 mg qid) + probenecid (500 mg qid) for 28 days (2) IM SSG (20 mg Sb/kg/d) with no upper limit on daily dose for 20 days	No treatment	365	Cure (45 days)	CR: 75 (Experiment) CR: 100 (Control)
Kopke et al., 1991 (Brazil)	30 (16, 14)	MA 14 mg/kg/day for 20 days	MA 28 mg/kg/day for 20 days	365	Cure	CR: 73 (Experiment-1) CR: 59 (Experiment-2) CR: 27 (Control)
Navin et al., 1990 (Guatemala)*	66 (22, 22, 22)	(1) IM MA 850 mg daily for 15 days (2) 30 seconds of 50°C localized heat, 3 treatments with 7-day intervals	Placebo	365	Cure (60 days)	CR: 30 (Experiment) CR: 100 (Control)

Saenz et al., 1990 (Panama)	52 (22, 19, 11)	(1) Oral ketoconazole 3 (200-mg tablets) before sleep each day (600 mg/kg/d) for 28 days (2) IM MA 20 mg/kg with a maximum of 850 mg/d for 20 days	Placebo	60	Cure (90 days)	17.22 (1.13, 262.82) (Experiment-1 and Control) 16.20 (1.06, 248.50) (Experiment-2 and Control) 1.06 (0.71-1.58) (Experiment-1 and Experiment-2)
Convit et al., 1989 (Venezuela)	217 (124, 51, 42)	(1) Vaccine consisting of killed <i>L. mexicana amazonensis</i> , and variable amounts of BCG (2) BCG alone in 2 sites in the deltoid regions, 3 doses at 6-8 wks intervals	IM MA, 50 mg/kg/d in 2-3 series of 20 daily injections, with (maximum dose: 3 g/d) with intervals of 15 days between successive series	730	Cure (180 days)	0.98 (0.90-1.06) (Experiment-1 to Control) 0.46 (0.32-0.65) (Experiment-2 to Control)
Convit et al., 1987 (Venezuela)	102 (44, 58)	Vaccine group: promastigotes of <i>L. mexicana amazonensis</i> + viable BCG, second dose after 6-8 wks, third dose after 12-18 wks	IM MA 50 mg/kg in series of 20 daily injections, with a maximum of 3 and a minimum of 2 series, and with 15 days between series	280	Cure (180 days)	0.93 (0.80-1.07)
Saenz et al., 1987 (Panama)	59 (30, 29)	IM SSG 20 mg/kg/d for 20 days (maximum daily dose: 850 mg)	IM MA 20 mg/kg/d for 20 days (maximum daily dose: 850 mg)	365	Cure	CR: 46.7 (Experiment) CR: 76.4 (Control)
Balou et al., 1987 (Panama)	40 (21, 19)	IV SSG 10 mg/kg/day 20 days	IV SSG 20 mg/kg/day 20 days	475	Cure	CR: 76 Experiment CR: 100 (Control)
Oster et al., 1985 (US)	36 (12, 12, 12)	(1) IV SSG 600 mg once per day for 10 days (2) IV SSG loading dose of 600 mg followed by 600 mg/d continuous infusion for 9 days	IV SSG loading dose of 600 mg followed by 200 mg every 8 hour for 9 days	365	Cure	CR: 100 (Experiment-1) CR: 50 (Experiment-2) CR: 42 (Control)

*Based on Gonzalez et al "Cure" has been defined as when all inflammatory signs have disappeared (either skin edema or hardening, or both), and that scarring or epithelialization has occurred in ulcerative lesions.²⁹ The figures in the parenthesis indicate the time point at which cure is defined in the primary study. † Studies in which both topical and systemic interventions have been used. FUD, follow-up duration; CR, cure rate; RR, relative risk; CI, confidence interval; qod, every other day; Sb, antimony; IV, intravenous; MA, meglumine antimoniate; IM, intramuscular; MBCL, methylbenzethonium chloride; bid, twice a day; SSG, sodium stibogluconate; GM-CSF, granulocyte colony stimulating factor; tds, three times a day; IFN- γ , Interferon gamma; qid, four times a day; wks, weeks; qd, daily; BCG, Bacillus Calmette-Guérin.

TABLE 28-6—Systemic Treatments of Mucosal Leishmaniasis (ML) Based on Gonzalez et al. and Amato et al. Systematic Reviews^{29,32}

Study & country	Sample size (experiment(s), control(s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome	RR (95% CI)
Llanos-Cuentas et al., 2007 (Peru)	38 (21, 17)	IM aminosidine sulfate 14 mg/kg qd for 21 days	IV MA 20 mg/kg in 250 mL 5%dextrose in water infused over a 20-minute period qd for 28 days	365	Cure*	0.05 (0.00, 0.78)
Machado et al., 2007 (Brazil)	23 (11, 12)	Oral pentoxifylline 400 mg tds for 30 days + IV SSG 20 mg/kg/d	Oral placebo orally tds for 30 days + IV SSG 20 mg/kg/d	730	Cure* at 4 months post-treatment	1.66 (1.03, 2.69)
Llanos-Cuentas et al., 1997 (Peru)	81 (40, 41)	IV SSG (20 mg of Sb ⁵⁺ /kg/d) plus oral allopurinol (20 mg/kg/d in 4 divided doses) for 28 days	IV SSG (20 mg of Sb ⁵⁺ /kg/d) for 28 days	365	Complete cicatrisation of the mucosal lesion 1 year post-treatment	0.62 (0.38, 1.03)
Franke et al., 1994 (Peru)	40 (20, 20)	IV SSG 20 mg/kg/d for 28 days	IV SSG 20 mg/kg/d for 40 days	365	Complete cicatrisation of the mucosal lesion 1 year post-treatment	0.83 (0.47, 1.47)

*Gonzalez et al. defined cure when all inflammatory signs disappeared and complete healing through either scar formation or complete re-epithelialization occurred.²⁹ FUD, follow-up duration; RR, relative risk; CI, confidence interval; IM, intramuscular; qd, daily; IV, intravenous; MA, meglumine antimoniate; tds, three times a day; Sb⁵⁺, pentavalent antimony; SSG, sodium stibogluconate.

considered while trying to figure out the best individualized therapeutic choice and management plan for every patient presenting with NWCL and/or mucosal leishmaniasis (ML).

Different types of treatment have been investigated in the above-mentioned systematic reviews. The Tuon et al. study is not a real systematic review of RCTs because less than half of all studies they have included are real RCTs.³¹

TABLE 28-7—Topical Treatments for NWCL Based on the Systematic Reviews of Gonzalez et al. and Tuon et al.^{29,31}

Study (Country)	Sample size (experiment(s), control (s))	Intervention(s) in experimental group(s)	Intervention(s) in control group(s)	FUD (Days)	Primary outcome*	RR (95% CI) or CR (%)
Lobo et al., 2006 (Brazil)	37 (17, 20)	Single session of heat therapy	IVMA 20 mg/kg/d for 20 consecutive days	28	Cure	CR: 59.0 (Experiment) CR: 10.0 (Control)
Soto et al., 2002 (Colombia)	45 (33, 12)	Topical WR279396 with 0.0005 mL/mm ² bid for 20 days	Placebo	200	Cure (70 days)	CR: 51.5 (Experiment) CR: 47.1 (Control)
Arana et al., 2001 (Guatemala)	76 (38, 38)	Topical 15% paromomycin + 12% MBCL bid for 20 days	Topical placebo (white soft paraffin) ointment	365	Cure	CR: 2.38 (1.50, 3.80)
Neva et al., 1997 (Honduras)	53 (23, 30)	Topical 15% paromomycin + 10% urea tds for 4 wks	Placebo	105	Cure (75 days)	CR: 4.3 (Experiment) CR: 3.3 (Control)

*Gonzalez et al. defined cure when all inflammatory signs disappeared and complete healing through either scar formation or complete re-epithelialization occurred.²⁹ FUD, follow-up duration; RR, relative risk; CI, confidence interval; CR, cure rate; IV, intravenous; MA, meglumine antimoniate; bid, twice daily; MBCL, methylbenzethonium chloride; tds, three times a day; wks, weeks.

The majority of the included RCTs in these reviews have been found to have moderate or low qualities and are prone to different kinds of bias. Therefore, the strength of resultant evidence is questionable.

Different treatment types will be categorized into four groups: pentavalent antimonials (meglumine antimoniate and sodium stibogluconate), paromomycin, azole agents, and miscellaneous treatments. As the authors have mentioned before in the treatment of OWCL section, there are some points, which need to be acknowledged while considering therapeutic options. In addition to the suggested points in the aforementioned section, the following should be considered regarding treatment of NWCL:

- The evidence on the therapeutic interventions for ML is limited and not substantial.
- There is lack of good quality evidence on treatment modalities such as azoles, amphotericin B, healing promoting therapies, and alternative therapy.
- Only about 30% and 13% of studies investigated by Gonzalez et al. properly reported randomization and allocation concealment methods, respectively.²⁹
- There are few high-quality studies amongst those included in the systematic review. Gonzalez et al. have only ranked two studies as high-quality studies in terms of randomization, allocation concealment, blinding and intention-to-treat. These studies were on patients infected with *L. mexicana*, *L. chagasi*, and *L. panamensis*.²⁹

PENTAVALENT ANTIMONIALS

Antimonials are still more effective than other therapeutic choices except pentamidine. Choosing between pentamidine and antimonials should be based on the region and the responsible species. It has been proposed that perhaps in cases of CL recurrence, pentamidine would be preferred to repeating antimonials.³¹

There are differences regarding drugs efficacy in different regions and with different *Leishmania* species. Based on the evidence from Colombia and Panama, when the causative organism is *L. braziliensis* or *L. panamensis*, intramuscular meglumine antimoniate and intravenous meglumine antimoniate do not increase cure rates when compared to placebo or no treatment.^{80,81} Intramuscular meglumine antimoniate does not provide significantly higher cure rates than placebo.⁸² No advantage is reported for either the 10-day or the 20-day regimens of intravenous meglumine antimoniate or intramuscular meglumine antimoniate when the causative agent is *L. braziliensis*, *L. panamensis*, or *L. mexicana*.⁸³ Also, 40 days of intravenous meglumine antimoniate treatment has no benefit over the 28-day regimen when the species is *L. braziliensis*. Other different dosages and/or regimens do not usually differ among treatment and control groups. This means that increasing or

decreasing the routine dosage and/or duration of treatment often fails to provide a clinical benefit over the current methods.⁸⁴⁻⁹³ However, there have been some exceptions to this fact, such as having significantly higher cure rates in 20-day intravenous meglumine antimoniate regimen versus 7-day intravenous meglumine antimoniate regimen when the organism is either *L. braziliensis* or *L. panamensis*.⁹⁴ In addition, when the organism is either *L. braziliensis* or *L. panamensis*, some additional benefits (i.e., synergism), are found while combining antimonial therapies with some other treatment modalities, such as combination of oral allopurinol and either intravenous meglumine antimoniate or intravenous sodium stibogluconate for 15 days or combination of oral pentoxyfylline and intravenous sodium stibogluconate for 30 days (*L. braziliensis* only). Other combinations including INF-γ, paromomycin 15% + methylbenzethonium chloride 12%, and imiquimod (5% or 7.5%) provided no extra benefit.²⁹

L. braziliensis, *L. amazonensis*, and *L. guyanensis* do not differ in terms of responding to antimonials.²⁹ This is true for other species as well; though they have not undergone analysis.

The branded meglumine antimoniate and generic sodium stibogluconate have been compared in terms of efficacy and side effects in few RCTs from Brazil and Colombia. They have been found to be equally efficient, although the sodium stibogluconate had more side effects.³¹

Tuon et al.³¹ have found no differences in terms of response to antimonials amongst the species they have found in their investigated studies (*L. braziliensis*, *L. amazonensis*, and *L. guyanensis*). There are some possible explanations for the differences observed in the response to antimonials in different regions and in different studies. These include: differences in host immunology, discrepancies amongst different *Leishmania* subspecies or strains, current diagnostic methods which can not define differences between *Leishmania* species (such differences have been shown using PCR), possible changes implemented by the *Leishmania* organism infected with *leishmania* virus, parasite intrinsic factors including its sensitivity to drugs, and primary resistance which is found in 14% of cases.³¹

Paromomycin (aminosidine)

Topical paromomycin in methylbenzethonium chloride provides significantly higher cure rates for *L. braziliensis* and *L. mexicana* infections when compared to placebo.²⁰ Tuon et al.³¹ do not suggest the isolated usage of topical paromomycin as a first-line therapy. A negative point with this drug is that it does not prevent the progression of CL into ML. However, when considering the fact that less than 5% of CL cases evolve into ML, the usage of paromomycin can be negotiated. A meta-analysis on the efficacy of paromomycin in comparison antimonials reported the odds ratios (ORs) (95% confidence interval [95% CI]) of

TABLE 28-8—Adverse Effects Reported in RCTS Conducted for OWCL Treatment Based on the Systematic Review by Gonzalez et al.³⁰

Intervention	Adverse Events
Pentavalent Antimonials (MA and SSG)	Pain at injection site, undefined local reactions, skin eruption, allergic maculopapular rash, sensitivity, pruritus, redness and swelling after the injection, edema, scaling at the periphery of site of injection, generalized muscular pain and weakness, sporotrichoid dissemination as satellite lesions, severe itch around the lesions, bradycardia or tachycardia, palpitation, local chest pain, headache, diarrhea, liver abnormalities, cough
Azoles (oral)	Nausea and vomiting, headache, dizziness, abdominal pain, increased liver enzymes
Paromomycin (topical)	Local reaction (inflammation, vesiculation, pain and/or redness), contact dermatitis, discharge, edema, pruritus, erythematous reaction, urticaria, lymphadenitis
Miscellaneous	
Allopurinol (oral)	Local reaction (inflammation, vesiculation, pain and/or redness), contact dermatitis, discharge, edema, pruritus, erythematous reactions, urticaria, lymphadenitis
Antifungals (topical)	Mild pruritus
CO² laser	Hyperpigmentation, persistent redness, hypertrophic scarring
Cryotherapy	Post-inflammatory hyperpigmentation, erythema, edema
Dapsone (oral)	Nausea, anemia
Healing promoting treatments	Drying of ulcers and skin surrounding them, mild burning sensation
Hypertonic NaCl (IL)	Pain at the injection site, sporotrichoid dissemination
Imiquimod (topical)	Moderate pruritus and burning sensation
INF-γ	Pain at the injection site, headache
Miltefosine (oral)	Nausea and/or vomiting, abdominal pain, diarrhea, cough, headache, pruritis, fever
Rifampicin (oral)	Elevated liver enzymes
Thermotherapy	Second-degree superficial burns
Zinc sulphate (IL)	Pain or burning sensation at injection site which can result in vasovagal shock inflammation
Zinc sulphate (oral)	Nausea and/or vomiting, leishmanid reaction and edema

MA, Meglumine antimoniate; SSG, sodium stibogluconate; IL, intralesional.

TABLE 28-9—Adverse Effects Reported in RCTS Conducted for NWCL Treatment Based on the Systematic Review by Gonzalez et al.²⁹

Intervention	Adverse events
Pentavalent antimonials (MA and SSG)	Myalgia, arthralgia, anorexia, malaise, mild-to-moderate muscle and joint stiffness, nausea, abdominal pain, headache, shortness of breath, mild elevations in liver enzymes, elevated triglyceride level, elevated creatine phosphokinase (CPK) level, fever, flu-like symptoms, pain at injection site, phlebitis at injection site, asthenia, pruritus, allergy, macular erythematous rash, herpes zoster, ECG abnormalities such as augmentation of QT interval in ECG, mild leucopenia, eosinophilia, and metallic taste
Azoles	Mild elevation of liver transaminases, fever, abdominal pain, nausea, headache, malaise, rash, dizziness
Paromomycin	Local pruritus, burning sensation, local pain, local edema, inflammation, soreness, redness, heat, exudation, fever, weakness
Miscellaneous	
Allopurinol (oral)	Mucocutaneous disease development within three months, headache, epigastric pain, eosinophilia, macular erythematous rash, herpes zoster, arthralgia, myalgia, fever and/or chills, abdominal pain, anorexia, thrombocytopenia
Aminoglycoside WR279396	Local reactions, moderate erythema

(Continued)

TABLE 28-9—Adverse Effects Reported in RCTS Conducted for NWCL Treatment Based on the Systematic Review by Gonzalez et al.²⁹ (Continued)

Intervention	Adverse events
Aminosidine sulphate	Increases in aspartate aminotransferase, myalgia, arthralgia, asthenia, anorexia, fever and/or chitis, pain at injection site
Imiquimod (topical)	Localized pruritus, erythema, edema, elevated liver enzymes, burning, local pain
INF-γ	Mild malaise, fever and/or chills and headache
Miltefosine (oral)	Nausea and/or vomiting, diarrhea, motion sickness, headache, increase in creatinine level, increases in aspartate aminotransferase or alanine aminotransferase
Pentamidine isethionate	Gastrointestinal events, musculoskeletal events, lesion pain, headache, paresthesia, weakness, fever and/or chills, bad taste, cough
Pentoxifylline (oral)	Nausea, arthralgia, dizziness, abdominal pain, diarrhea
Thermotherapy	Moderately severe local cellulites, superficial second-degree burn, secondary bacterial infection after treatment
Vaccine	Shallow necrosis and ulcers at inoculation site, headache, fever, bone and muscle pain, hypotension, cardiac rhythm disturbances, paresthesia, severe colic, pain at injection site

MA, meglumine antimoniate; SSG, sodium stibogluconate; ECG, electrocardiogram

0.25(0.12-0.49) and 0.55 (0.31-0.99) for topical and intravenous paromomycin, respectively.³¹ Ten days of topical paromomycin plus methylbenzethonium chloride plus 3 or 7 days of intravenous meglumine antimoniate had significantly lower results compared to intravenous meglumine antimoniate for 20 days. Topical paromomycin plus methylbenzethonium chloride plus 7 days of intravenous meglumine antimoniate had significantly higher results compared to this regimen for three days.⁹⁵ Other regimens or combinations of paromomycin did not result in significant differences.^{96,97}

A recent meta-analysis on topical paromomycin in CL has reported that topical paromomycin was less effective in NWCL compared to pentavalent antimonials. In addition, there was no significant difference between parenteral paromomycin and antimonials in terms of their effectiveness in NWCL.⁸⁰

Azoles

Although oral ketoconazole has been reported to be significantly more effective than placebo for treating NWCL caused by *L. panamensis* and *L. mexicana*, it provided no added benefit when compared to intramuscular meglumine antimoniate.⁸¹ Oral ketoconazole effectiveness was neither significantly higher than intramuscular meglumine antimoniate nor intravenous sodium stibogluconate.^{81,98} In a meta-analysis, the efficacy of azoles versus antimonials was investigated and an OR (95% CI) of 0.05 (0.01-0.09) was reported.³¹

MISCELLANEOUS

In infections by *L. braziliensis* and *L. panamensis*, there are controversial reports on the efficacy of oral allopurinol

when compared to antimonial therapy. One study reported that it was more efficient than intravenous meglumine antimoniate and than no-treatment, while it lost its effectiveness when combined with intravenous meglumine antimoniate. It had a synergistic effect when combined with intravenous meglumine antimoniate. Oral allopurinol plus intravenous meglumine antimoniate was reported to be significantly more effective than no treatment, while another study showed no significant difference in this regard. Also, allopurinol had significantly higher cure rates compared to no treatment.^{80,98,99} One study has reported that the aforementioned intervention even had lower efficacy in comparison with intramuscular meglumine antimoniate.⁸¹ It is a possibility that the route of prescribing antimonials is an important factor while assessing their efficacy versus allopurinol in a way that allopurinol has been more effective when antimonials are given intravenously and its efficiency decreases when antimonials are administered intramuscularly. In other regimens or combinations, there was no significant difference in primary outcome.^{87,100,101} In a meta-analysis the OR (95% CI) favoring allopurinol was 0.31 (0.18, 0.55).³²

There have been contradicting results about the efficacy of oral miltefosine in comparison with placebo. While one study showed significantly higher effectiveness, the other did not support this finding. This is possibly dependent upon the region and/or the species (*L. panamensis* vs. *L. braziliensis* and *L. mexicana*).¹⁰²

The suggested regimen for intramuscular aminosidine sulphate has been 18 mg/kg/d for 14 days since the 12 mg/kg/d regimen for 7 days has been shown to provide patients with lower cure rates. No other significant differences in terms of effectiveness or even lower cure rates has been reported for other intramuscular aminosidine sulfate regimens in other studies.¹⁰³⁻¹⁰⁵ The cure rate for intramuscular

aminosidine sulfate with the dosage of 14 mg/kg/d for 21 days was reported to be significantly lower than that of intravenous meglumine antimoniate with the dosage of 20 mg/kg/d for 28 days.¹⁰⁶

Intravenous pentamidine isethionate has been studied in cases of infection with *L. braziliensis* and there has been significantly lower cure rates for it when compared to intravenous meglumine antimoniate. Intramuscular pentamidine isethionate does not provide significantly higher cure rates compared to intramuscular meglumine antimoniate.^{105,107}

Topical aminoglycoside WR279396 did not show significantly higher cure rates compared to placebo.¹⁰⁸

Thermotherapy alone or in combination with antimoniais has not been proved to provide significantly higher cure rates than placebo or antimoniais.^{82,109}

Immunotherapy with vaccine and intradermal BCG have been found to have similar or significantly lower cure rates when compared to intramuscular antimoniais.¹¹⁰⁻¹¹²

Topical imiquimod 5% and 7.5% alone or combined with antimoniais, have been reported to have no significantly higher cure rates when compared to intravenous meglumine antimoniate in different species.^{113,114}

Subcutaneous INF- γ combined with intramuscular meglumine antimoniate has been reported to provide no higher cure rates compared to either 10-day or 20-day intravenous meglumine antimoniate.¹¹⁵

In the studies on the efficacy of topical or intralesional granulocyte macrophage colony stimulating factor (GM-CSF), combined with antimoniais compared to either placebo or intravenous antimoniais, no statistically significant difference has been reported.^{116,117}

A synergistic effect has been reported for oral pentoxifylline combined with intravenous sodium stibogluconate 20 mg/kg/d both for 30 days.¹¹⁸

ADVERSE EFFECTS

Gonzalez et al. have reported the adverse effects of therapeutic interventions, which was reported in the RCTs and included in their systematic reviews.^{29,30} These adverse effects are summarized in Tables 28-8 and 28-9 for the treatment of OWCL and NWCL.

SUMMARY

Despite existence of a large number of RCTs and publication of five systematic reviews, the bottom line of an evidence-based approach to the treatment of different types of CL can be summarized in the following sentence: "No high level evidence is available for the treatment of OWCL and NWCL." As Khatami et al. and Gonzalez et al. have mentioned in their systematic reviews, most of the conducted trials are of poor quality.^{29,30,33} Pentavalent antimoniais, which have been even considered as first-line treatment by some sources,¹¹⁹ can only be administered parentally, are associated with several adverse effects and not affordable for the majority of developing countries in which the disease is prevalent. Drug resistance to pentavalent antimoniai has also been reported and is an important issue for future research.^{120,121}

In order to combine the current best research evidence with some important practical issues regarding treatment of CL, an evidence-based clinical practice guideline has been developed in Iran, where it is endemic for CL because of *L. tropica* and *L. major*.¹²² In spite of its potential benefit for the country for which it has been developed, clinical practice guidelines should always be meticulously tailored for use in other countries.

Acknowledging the fact that still no effective and safe preventive intervention exists for CL, the need for

What We Know: Therapeutic Modalities for OWCL

Therapeutic modality*

Pentavalents antimoniais (either intralesional or systemic)

Topical paromomycin

Cryotherapy + intralesional meglumine antimoniate

Oral fluconazole

Oral itraconazole

Photodynamic therapy (PDT)

Thermotherapy

Oral pentoxifylline (as an adjuvant to intramuscular meglumine antimoniate)

Topical clotrimazole

Intralesional zinc sulfate

Other interventions

Strength of recommendation†

A

B

B

B

B

B

B

C

D

I

*All interventions are pertinent only for infection because of *L. major* with the exception of intralesional or systemic administration of pentavalent antimoniais, which may be used for infections attributed to either *L. major* or *L. tropica*.

† The strength of recommendations was addressed based on the U.S. Preventing Services Task Force (USPSTF) standards.¹²⁵

What We Know: Therapeutic Modalities for NWCL/MCL/ML

Therapeutic modality*	Strength of recommendation†
Systemic pentavalent antimonials	A
Topical paromomycin	B
Oral ketoconazole	B
Oral allopurinol (as an adjuvant to either intravenous meglumine antimonate or sodium stibogluconate)	C
Oral pentoxifylline (as an adjuvant to intravenous sodium stibogluconate)	C
Other interventions	I

*All interventions are pertinent for infections due to *L. braziliensis*, *L. panamensis*, or *L. mexicana* except oral pentoxifylline which is only pertinent to infections caused by *L. braziliensis*. Often modalities have been studied on other species as well including *L. guyanensis*, *L. peruviana*, and *L. chagasi*; however, these species have been investigated in fewer studies.

† The strength of recommendations was addressed based on the U.S. Preventing Services Task Force (USPSTF) standards.¹²⁵

properly designed, conducted, and reported RCTs with large sample size and clinically meaningful outcome measures is obvious. Performing such RCTs and consequently conclusive systematic reviews through updating current ones and or conducting new ones cannot be overemphasized for providing reliable strong evidence for treatment of this neglected but important disease.^{8,33,123,124}

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Treatment of Head Lice

29

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INTRODUCTION

Head lice, are bloodsucking, wingless insects belonging to the order Anopura.¹ Pediculosis, the infestation of humans by lice, has been documented for thousands of years.² They are host specific so, *Pediculus humanus capitis*, the head louse, cannot be transmitted to or from pets or other animals.

Infestation with head lice is on the rise in the United States and worldwide. Well over a decade ago it was estimated that \$367 million was spent annually on the eradication of 12 million infestations in the U.S. alone.³ However today, because of the accelerating rate of resistance to most over-the-counter (OTC) pediculicides and the fact that patients use these remedies an average of five times before seeking treatment from a healthcare professional, no one can be sure how large that Infestation rate has grown.⁴

EPIDEMIOLOGY

School-aged children between 3 and 11 years, as well as their immediate contacts (such as day care providers, playmates, and family members) remain the most likely targets for infestation. The relatively high incidence of head lice in this group is probably related to head-to-head contact during play and the sharing of objects to which lice cling (e.g., naptime, combs, brushes, hats, barrettes, helmets, head phones, and other head gear). Mumcuoglu et al. found that children with longer and medium hair length were more often infested than children with short hair.⁵ In contrast to body and crab lice, which have given head lice a bad reputation, they are not linked to poverty, poor living conditions or refugee status, and are most commonly found in individuals in good health, with good hygiene and grooming habits.⁶

In the United States, head lice infest all levels of society and most ethnic groups. They can be found among Caucasians, Asians, Hispanics, and North, Central, and South American Indians. In the past the notable exception was the African-American population, where prevalence was so low that it was recommended that this ethnic group be excluded from prevalence estimates. In a 1977 study, Juranek found pediculosis capitis in only 0.3% (6/1853) of African-American children compared with 10.4% (573/5513) of other races.⁷ It is believed that the head louse indigenous

to this part of the world is not well adapted to grip the oval-shaped hair shaft characteristic of the hair found in the African-American population.⁸ In Africa, where the head lice have claws adapted to tightly curled, oval-shaped hair, pediculosis capitis is a serious problem among blacks.⁹

However, we have seen an increase in cases in this population in recent years. In our experience, in the Miami area more African-American children are infested with lice than in the past, and anecdotal evidence suggests that this may be an emerging trend nationwide. This may be attributed to the adaptation of the louse, changes to the hair structure caused by the blending ethnicities of the host as well as the increased global travel of mankind. Although the prevalence among African-Americans seems to be increasing, infestation in this population is still well below that in other races in the United States.

ETIOLOGY AND DIAGNOSIS

Pediculosis capitis is the term applied to infestation of the scalp by the human head louse, *Pediculus capitis*. Individual sites of feeding are difficult to see. There may be signs of irritation in the form of erythema, scaling, scabbing, pyoderma and the periphery of the hairy areas may exhibit linear excoriations. Pruritus is a common symptom in subjects who have had head lice for several weeks, but first-time infestations may not produce any symptoms. Individuals who have had previous episodes usually develop pruritus within 48 hours of exposure. Some conditions that can give a false diagnosis of pediculosis include contact or seborrheic dermatitis, insect and mite bites, eczema, psoriasis, or piedra.

Most cases of head louse infestation in schools are first detected by observations of one or more children scratching their heads. Closer scrutiny may reveal nits adherent to the hairs. Usually, these are the whitish to sandy-colored empty shells of eggs that have hatched. It is common for desquamated epithelial cells (DEC) or pseudonits (commonly known as "hair muffs" or hair casts) to be mistaken for eggs. Newly laid or viable intact eggs are more difficult to see, and may be tan to coffee-colored or darker with a black "eye spot".¹⁰ In colder climates viable nits will be found close to the scalp. However, this may not be true in warmer climates where body heat is not needed for incubation and may actually provide too much heat.¹⁰

As soon as a nit hatches, the 1st instar nymph, which is only 0.5 mm in length, will travel to the scalp to feed and stay for approximately 6 days. As it grows to adulthood, it becomes more adventurous and travels around the scalp and hair. The most definitive tool for diagnosis is the identification of live lice. However, because lice move quickly, avoid light, and tend to take on the hair color of their host (i.e. blonds will have lighter lice than brunettes), lice can be difficult to find. The most common places to find them are behind the ears and at the nape of the neck.¹¹

LIFE CYCLE

Just before hatching, the louse embryo uses its chitinous mouth parts to cut a hole in the operculum (the cap of the egg), which always faces away from the scalp. The newly emerged baby louse, also known as a nymph or “instar”, must feed on human blood shortly after hatching to avoid starvation or dehydration, and will feed on blood every 4 to 6 hours for the remainder of its life. Lice rarely live for more than 24 hours away from the host without a human blood meal.¹² The louse goes through three stages of development which each last 3 to 4 days, prior to reaching adulthood. During this development, the first, second and third instar stages, the louse molts, and casts off its exoskeleton to reveal a new one.

The sex is not determined until adulthood, approximately 9 to 12 days after hatching. The appearance and shape of the two different sexes are distinctively different. Females are usually 20% larger than males, although variations can occur. Females are not only usually longer, but wider and rounder than males, with a posterior portion that terminates in two protrusions, creating an invaginate V shape. The abdomen of females contains one to three fully formed eggs and the female head louse will lay 5 to 10 eggs a day throughout her lifetime of about 30 days. By contrast, the smaller male has a rounded posterior and brown bands across the back that darken with age. Adult lice are approximately the size of a sesame seed, ranging from 2.1 to 3.3 mm.¹¹

DISEASE TRANSMISSION

Unlike body lice, head lice, are not known to be vectors of disease. However, head lice have been shown to transmit *Staphylococcus aureus* and group A *Streptococcus pyogenes*.¹ In a homeless population in California, Bonilla et al. found that 25% of head lice-infested persons had lice pools infected with *Bartonella quintana* strain Fuller, the bacterium that causes trench fever in humans.¹³

TREATMENTS

Effective treatments to remove lice and nits include include nit-combing, brushing, and/or application of pediculicides (Table 29-1). Most pediculicide products currently

available in the United States kill lice but not their eggs. Therefore, if lice are present 8-12 days later, a second treatment should be applied to kill any nymphs that may have hatched from eggs that survived the first treatment.

The rise in head lice resistance to OTC products currently makes treatment options difficult. The active ingredients of the pediculicidal products currently available in the United States include lindane, natural pyrethrins, permethrin, and malathion. These and other alternative head lice treatments and emerging products are discussed in detail below.

Prescription Products

Benzyl Alcohol Lotion 5%

The non-pesticide asphyxiant, Benzyl Alcohol Lotion 5% (Ulesfia™) is the first head lice treatment to be approved by the Food and Drug Administration (FDA) since 1986. It is approved for two 10-minute treatments applied 1 week apart. Scanning electron micrographs (SEM) indicate that unlike other asphyxiants which cause the louse to simply close down its respiratory system, Benzyl Alcohol Lotion 5% (BAL 5%) suffocates lice by stunning the apparatus open allowing the vehicle to infiltrate and decimate the “honeycomb” structure lining the breathing spiracle.¹⁴ Clinical trials showed two treatments of BAL 5% to be 75% effective. This novel nontoxic pediculicide can be used on the most vulnerable populations including children as young as 6 months of age. This product is an easy to use water-based lotion with a consistency similar to hair conditioner.

Malathion

Malathion is an organophosphate and an irreversible cholinesterase inhibitor. Illnesses linked to agricultural use of this pesticide have raised concerns about its toxicity in humans. However, the high grade of malathion used for the treatment of human pediculosis is very different from the grade used for agricultural or veterinary purposes.¹⁵

In the United States, 0.5% malathion lotion (Ovide®; originally known as Prioderm®) is the quickest acting and most ovicidal of any pediculicide developed in the last 30 years.^{16,17}

Ironically, despite its quick action, Ovide® is labeled for a relatively long application time. Because the original malathion studies for FDA approval involved an 8-12 hour application, this became the recommended treatment protocol. The 78% isopropyl alcohol content, longer application time, and limited use to 6 years and older, are potentially undesirable attributes. We found that a reduced application time of 20 minutes is equally effective and is significantly more pediculicidal and ovicidal than Nix®.¹⁸

Resistance to malathion products other than Ovide® has been documented in many countries including England.¹⁹ In the UK and other countries where two products have been combined, such as malathion and permethrin, lice are still resistant. So far there are no documented cases of resistance in the United States. Lice in the USA may have remained sensitive to malathion because this product is not as readily available as it is in the UK and other countries, where it can be purchased over the counter. Also, the formula available in the United States is different than in other countries and incorporates a resistance strategy component.

Lindane

Lindane 1% (gamma-benzene hexachloride, GBH, GBHC, formerly known as Kwell®) has been available as a shampoo for the treatment of head lice for more than 50 years. Although 1% lindane shampoo is simple to use, with a recommended treatment time of only 4 minutes, it has serious drawbacks. Lindane belongs to the class of chemical insecticides called organochlorines, which also includes DDT. These insecticides do not degrade and thus persist in the environment for decades. Lindane rinsed off after use passes through the sewer system into creeks, rivers, lakes and oceans, where it can contaminate drinking water, the tissues of fish and wildlife, as well as farm soil. For these reasons, California banned the sale of all lindane products in that state beginning in 2002. Lindane not only persists in the environment but also accumulates in the body, especially the central nervous system, creating the potential for risk of serious neurotoxicity.^{20,21}

One disadvantage of lindane for treatment of head lice is its slow killing time which can last up to 6 hours. Additionally, lindane has a high treatment failure rate, because of tolerance or resistance in lice. In 2003 the Food and Drug Adminstration (FDA), "black boxed" lindane, meaning that its website and labeling warns against using the product because of toxicity, specifically for anyone under 110 lbs.²² In view of the many negative aspects of this pediculicide, it is difficult to see the advantage of future lindane use, particularly when several other less toxic and more effective treatments are available.

Carbaryl

Carbaryl (1-naphthyl N-methylcarbamate, marketed as Carylderm, Derbac, Sevin, and generics) is a prescription second line treatment for pediculosis capitis in the United Kingdom and Australia, where it is available in both a 0.5% lotion and a shampoo formulation. It is a reversible cholinesterase inhibitor with an objectionable odor. Like lindane, it has been banned for both human and agricultural uses in many countries.

Prescription Products Off-Label

Ivermectin

While the FDA has approved oral ivermectin for the treatment of internal parasitic infections onchocerciasis and strongyloidiasis, this drug does not have an FDA-approved indication for the treatment of head lice. However, ivermectin has been used "off label" for pediculosis treatment when all other treatments have failed. Since the half-life of ivermectin in the bloodstream is only 16 hours, it is necessary to give more than one dose in order to kill nymphs that hatched from the eggs. Ivermectin is not ovicidal.

Unpublished studies by Meinking et al.^{23,24} conclude that oral ivermectin is safe, well tolerated and most effective in killing head lice at the dose of 400 µg/kg, on days 1 and 8.

Cotrimoxazole

Reports have appeared suggesting that oral administration of cotrimoxazole (sulfamethoxazole/trimethoprim, TMPX, Septra, Septrin, Bactrim and different names in various countries) is an effective treatment for pediculosis capitis.^{25,26} Because lice are obligate blood feeders and are dependent on their symbiotic bacteria for survival, these reports may indeed have merit. However, this is not a fast-acting pediculicide and it should only be prescribed when pyoderma, ear infections, and other indications for this antibiotic warrant it.

Cotrimoxazole is a valuable antibiotic combination that should be reserved for significant infections. Also, in rare cases, this drug may produce harmful side effects, including allergic reactions, aplastic anemia, toxic epidermal necrolysis (TEN), and blood dyscrasias.

Prescription Products in Development

Topical Ivermectin

Topical ivermectin for the treatment of head lice was found to be effective in Alexandria, Egypt. 1% ivermectin lotion had a curative effect on head lice after a single application. Youssef et al.²⁷ reported that a single application of 0.8% ivermectin lotion was effective in treating head lice in all 25 patients treated with clearance of lice within 48 hours after application. A 0.8% ivermectin shampoo was more effective than a shampoo containing 1% lindane in 208 Columbian patients.²⁸ Even though more clinical trials are needed to confirm this efficacy, topical ivermectin provides a promising alternative therapy for head lice, particularly with resistance to current available topical treatments on the rise.²⁹

Spinosad

Spinosad has been approved by the Environmental Protection Agency (EPA) as a crop protection product in

TABLE 29-1—FDA-Approved Therapy for Head Lice Infestations

Approved Therapy	1% Lindane	0.5% malathion	Natural pyrethrins with PBO	1% permethrin	Ulesfia™ (benzyl alcohol) Lotion
Pediculicide Classification	Organochlorine	Organophosphate	Plant extract with synergist (piperonyl butoxide)	Synthetic pyrethroid	Asphyxiant
Recommended application time	4-10 minutes (two applications one week apart)	Package insert 8-12 hours, effective in 20 minutes	10 minutes (two applications one week apart)	10 minutes (two applications one week apart)	10 minutes (two applications one week apart)
Killing time	6-24 hours	5-20 minutes	3-28 hours	3-30 hours	10-30 minutes
% Ovicidal activity	10-24	98-100	30-60	30-70	70-80
Residual activity	No	Yes-only if applied for at least 6 hours (not recommended)	No	Yes-only in sensitive populations	No
Cosmetic acceptability	Fair	Poor	Good	Good	Excellent
LD 50 mg/kg (rats)					
Oral	88	2800	584 - 900	3185	1230 – 3200
Dermal	1000	4400	1500	Over 5000	NA*
Adverse properties	Banned in some states/countries due to contamination of drinking water, CNS toxicity, overuse due to ineffectiveness, delusions of parasitosis	Irreversible cholinesterase inhibitor, flammable, unpleasant odor	Allergic reactions in people with certain flower allergies	No substantial reports	No
Resistance Reported	Worldwide	Europe, Middle East, and other places worldwide (not USA)	USA and other countries worldwide	USA and other countries worldwide	No
Trade names	1% Lindane Shampoo	Ovide (USA only)	RID and generic versions (generics are more effective)	Nix crème rinse and generics	Ulesfia™ (benzyl alcohol) Lotion

*No dermal LD₅₀ were conducted in rats. In rabbits, 10% solution of benzyl alcohol did not produce dermal irritation after a single 24-hour exposure. The MTD of benzyl alcohol in rats when administered dermally was 1000 mg/kg/day.

the United States, Canada, and Australia, and has received provisional approval in the UK, Spain, and several other European Union countries. In 2002, the National Organic Standards Board approved Spinosad's use in the production of certified organic foods. The product is used to eliminate pests in crops. It is not based on a synthetic compound, but on bacteria that occurs naturally in soil in the Caribbean. Phase III trials found spinosad, without combing, well-tolerated and demonstrated superiority to 1% permethrin with combing. The results of the trial found a total of 84.6% (study 1) and 86.7% (study 2) spinosad-treated subjects lice-free 14 days after final treatment and the majority one treatment only.³⁰

Over-the-Counter Products

Pyrethrins (natural plant extracts)

Extracts of the flower heads of *Chrysanthemum cinerariaefolium* contain a mixture of active agents called natural

pyrethrins, which include pyrethrin I, pyrethrin II, jasmolin I, jasmolin II, cinerin I, and cinerin II. These extracts are available in lotion, shampoo, foam mousse, and gel formulations that also contain the synergist piperonyl butoxide (PBO; RID®) is a natural extract. All natural pyrethrin products manufactured since 1950 are combined with piperonyl butoxide (PBO), which has insecticidal properties of its own, greatly enhancing the activity of pyrethrins and reducing the amount necessary while providing the same activity. Originally, it was added purely for financial reasons but it has been found to block the mixed function oxidase (MFO) pathway of resistance. The active agents in the pyrethrum flowers are extracted with kerosene or petroleum distillates, which may cause eye irritation. The natural pyrethrins demonstrate low mammalian toxicity (600–900 mg/kg oral, 1500 mg/kg dermal calculated as LD₅₀). They suffer, however, from poor stability to heat and light and have no residual activity.

None of the natural pyrethrin pediculicides are totally ovicidal. Twenty to 30% of the eggs of the head lice remain

viable after treatment.^{16,31} This necessitates a second treatment 7–10 days later in order to kill newly emerged nymphs, hatched from eggs that survived the first treatment.

Apart from the inconvenience and expense of having to treat twice, there is no evidence that multiple treatments with pyrethrins is hazardous. As with all topical agents, repeated use invites the development of cutaneous allergic reactions, contact dermatitis, and dry itchy scalp, which may be mistaken as a treatment failure.

Permethrin (a synthetic pyrethroid)

By synthesizing and modifying the molecular structure of natural pyrethrins, chemists were able to develop compounds called pyrethroids. Permethrin (3-phenoxybenzyl(1, 2)-3-(2,2-dichlorovinyl)-2,2 dimethyl cyclopropane carboxylate), is the first heat and light-stable synthetic pyrethroid, and has even lower mammalian toxicity than natural pyrethrins. Based on oral studies in animals, this compound is about three times less toxic than natural pyrethrins and approximately 36 times less toxic than lindane.

In the United States, permethrin is available as a 1% cream rinse (Nix®, generics). In some other countries, preparations of both strengths are available over the counter. The 1% permethrin creme rinse (Nix) has been approved by the FDA for the treatment of pediculosis since 1986. This product has undergone more clinical trials and toxicology studies than any other pediculicide on the US market. Like the natural pyrethrin products, Nix® is not completely ovicidal; approximately 20–50% of viable eggs hatch after treatment. Also, although residual permethrin on the hair once killed nymphs soon after they hatched, this is no longer the case. They have become resistant to any residual effect. Data from the U.S. and numerous countries indicates that resistance has become a worldwide problem.³² Recent studies in the United States have not only confirmed the existence of permethrin resistance, but also traced this resistance to specific genetic mutations in lice.³³ Because of the prevalence of resistance, it has become necessary to apply Nix® two times, 1 week apart. However, even with two applications, Nix often is not effective in killing lice.¹⁸

Dimethicone

Dimethicone is a silicone-based treatment that is currently marketed in different concentrations and solutions in various parts of the world. Burgess³⁴ found that two applications of 4.0% dimethicone lotion cured 70% of study participants of head lice infestation. The product was kept on the hair for 8 hours or overnight. A second application is necessary because dimethicone is not ovicidal. Nymphs that hatch since the first application must be treated with a second application 1 week later. The product is applied to dry hair and shampooed or brushed out. Like benzyl

alcohol lotion 5%, dimethicone seems less irritating than existing treatments and has a physical action on lice that should not be affected by resistance to neurotoxic insecticides. However, it is not FDA approved and has not been tested for children younger than 4 years of age and because it is an emollient; very high concentrations of it are slippery, and special care should be taken to avoid spillage and injury from slips and falls.

Alternative Products

Since many frustrated parents and health professionals are reluctant to apply pesticides to children's heads, they have turned to alternative therapies to battle head lice.

Many claim to have successfully cured their infestations by using inexpensive, readily-available products from the grocery or health food store. There is no doubt that oily alternatives slow down the lice and make them easier to find and comb out. However, when these alternatives are rinsed off the next morning, the lice usually survives. Petroleum jelly (Vaseline) and mayonnaise are two alternative treatments that should be avoided, but for different reasons. Vaseline leaves behind a waxy residue that disguises the visual impact of nits. It also leaves the hair tacky, causing lint and other substances to stick to it. Mayonnaise, on the other hand can be dangerous. When left on the hair for a period of time, particularly in warm climates, it has been known to drip and get into the mouths of children, thus causing food poisoning.

Nit Picking

It is common practice to comb or “nit pick” through the hair after treatment to remove lice and nits. Nit removal is important for two main reasons. First, it removes an outwardly visible sign of head lice infestation, thus preventing stigmatization. Second, because no pediculicide kills 100% of eggs, manual nit removal is recommended to eliminate any nits that may have survived treatment.

However, many school authorities in the United States insist upon a “no nit” policy to ensure freedom from infestation and proof of adequate treatment. Under this policy, children with visible nits are sent home and parents are required to treat them so that they are nit-free before returning to school. However, this strategy does not work. Visible nits does not mean “viable” nits, nor does it necessarily mean the presence of live lice or an active infestation. Often what is identified by school officials as nits, are previously hatched out egg casings or displaced sebaceous plugs, also known as pseudonits. These desquamated epithelial cells encircle the hair and are usually the same size and color as a nit.

Neither the American Academy of Pediatrics (AAP), nor the Center for Disease Control (CDC)³⁵ recommends the “no nit” policy. In an AAP article, Frankowski et al.

What We Know

- Head lice are not a result of poor hygiene.
- The population most vulnerable to head lice infestation is children 3 to 11 years of age.
- Head lice are hemimetabolic in development, meaning that they do not go through a complete metamorphosis and that the larval stage of a louse merely looks like a baby adult. The life cycle of the louse is as follows:
 - It takes the egg 8 to 12 days to hatch,
 - The first “instar” or nymph takes 3 to 4 days to molt to the
 - Second “instar”, which then takes 3 to 4 days to molt to
 - The third “instar”, which takes 3 to 4 days to molt to
 - An adult (9 to 12 days after hatching) at which point its sex is determined,
- 2 days later it begins to copulate.
A louse lives approximately 30 days.
- Head lice have six legs and 14 breathing spiracles.
- Head lice do not fly.
- Unlike crab and body lice, head lice are not known for being vectors of disease, however they have been shown to transmit *Staphylococcus aureus* and group A *Streptococcus pyogenes*.¹ In a homeless population in California, Bonilla et al. found that 25% of head lice-infested persons had lice pools infected with *Bartonella quintana* strain Fuller, the bacterium that causes trench fever in humans.¹³
- Worldwide resistance has been a problem for decades. However, the introduction of new treatments seeking approval by the FDA offers hope of alleviating this problem for the future.
- Head lice can live 15 to 24 hours without a blood meal.

cited a study that followed 1729 school children screened for lice. Only 31% of the 91 children who had nits, also had live lice. And only 18% of those with nits alone developed to an active infestation over 14 days of observation.³⁶ Furthermore, banning children from attending school based on the presence of nits often results in parents missing work, which can create economic hardship for families. It is not necessary to cut long hair or shave the head to manage a head lice infestation. While such measures may ease the task of looking for and removing nits, the possible psychologic damage done by such shearing should override any potential benefits.

CONCLUSION

When head lice are found, parents often get angry or anxious and may even blame their child. Practitioners can help alleviate family anxiety and stigmatization by not only prescribing treatment, but easing blame and passing on some common sense. For example:

1. Head lice infestation is not caused by poor hygiene. It is most likely that the infestation occurred as a result of head-to-head contact, a sleep over, or a shared hat or batting helmet. Family members should be advised to avoid these behaviors in the future.
2. In addition to treating the family member(s), wash and dry their sheets, pillow cases, and towels.
3. Vacuum once.
4. Remember that lice do not last for more than 36 hours without a blood meal, nor do they fly. It is unlikely that lice will be found away from the hair on inanimate objects such as carpets or couches, and if they are, they will not live long. Don’t make yourself crazy cleaning.

Concentrate on monitoring the hair and scalp of the infested family member(s) and their siblings.

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Treatment of Scabies

30

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SEARCH METHODOLOGY

Data for this chapter were found through searches of Medline and Lilacs databases using the keywords "scabies" in combination with "treatment". Additionally, reference lists of retrieved articles were searched. No date restrictions were set in these searches. Articles in English, French, German, Spanish, and Portuguese were analyzed. References found in textbooks on parasitic skin diseases, and tropical medicine were also used. As a rule, only controlled clinical trials were included in this analysis.

INTRODUCTION

Scabies is an intensely pruritic skin disease caused by the infestation with *Sarcoptes scabiei var. hominis*. In industrial countries, the infestation occurs sporadically or in epidemics, such as in hospitals, nursing homes, or prisons. In the developing world, particularly in resource-poor urban and rural communities, the infestation is endemic. Globally, 300 million people are supposed to suffer from scabies.¹

Transmission of *Sarcoptes* mites requires intimate body contact such as between a mother and her child, during sexual intercourse, or when children play together with their body only partly covered by clothes. The role of fomites in transmission is discussed controversially.

TREATMENT OVERVIEW

Clinically, scabies presents in a variety of manifestations. There is reason to assume that scabies is an immune-mediated spectral disease with nodular scabies at one end of the spectrum and disseminated crusted (Norwegian) scabies at the other end². Depending on the immune competence of the host the propagation of the parasites is almost completely abrogated at one end of the spectrum (nodular scabies) and at the other end remains uncontrolled (disseminated scabies). Hence, for optimal treatment the immune competence of the patient has to be taken into consideration.

Immediate treatment of the patient, together with treatment of close contacts are the principles of case management. As contacts may be infested without presenting

signs or symptoms, they should be treated, independently whether scabies is suspected or not. Superinfection should be treated with a topical antibiotic.

Two to four weeks after treatment the patient has to be re-examined. Even after successful elimination of all mites, pruritic papules and nodules may persist for months. Another explanation of persisting itch and for eczema after effective therapy is the development of a contact dermatitis caused by the topical acaricide.

As compared to other parasitic skin diseases, evidence which treatment is optimal for a defined clinical condition or in a certain setting is rather scarce. A recent systematic review identified twenty small trials involving 2392 patients, the majority performed in developing countries.³ Methodologic quality varied considerably between trials. Only two trials described both adequate randomization sequence generation and adequate allocation concealment and the majority of the reports described neither adequately. The degree of blinding was unclear in eight of the 20 identified trials, and losses to follow-up were greater than 20% of the enrolled participants in three of the trials. The studies differed considerably with regard to setting, disease prevalence in the population, intensity of the infestation, outcome measure (such as parasitological cure, resolution of lesion, decrease of pruritus, etc.) and length of follow-up. This is of importance, since it may be expected that in an endemic area, reinfection is common and that reinfection may be indistinguishable from primary treatment failures.

Moreover, treatment regimen varied between the trial sites. For instance, benzyl benzoate was used in concentrations from 10% to 25%, and oral ivermectin was given in a single dose of 100 µg/kg, but also in two doses of 200 µg/kg given 8 to 10 days apart. Hence, although the studies analysed by Strong and Johnstone³ fulfilled the prerequisites of a randomized, controlled trial, reported cure rates have to be regarded with caution.

An overview of current treatment options is given in Table 30-1. Since the effectiveness of the various compounds seems to depend on the setting, treatment recommendations vary from country to country, and the selection of a drug is often based on the personal preference of the dermatologist, local availability of the drug and cost, rather than on sound evidence.

TABLE 30-1—Overview of Current Treatments for Scabies

Substance	Dosage	Advantages	Useful in Special situations	Resistance Known	Contraindications/disadvantages
Lindane	0.3-1% lotion or cream	Effective, inexpensive	No	Yes	Pregnant women, children/severe neurotoxic adverse events, particularly in children; substance is stored in fat cells and breast milk
Benzyl benzoate	10-25% ointment	Effective, inexpensive	Resource-poor settings	No	Pregnant women, infants/can cause severe skin irritation
Sulfur in petrolatum	2-10% liquid	Inexpensive	No	No	Infants, children/noxious and malodorous; may cause skin irritation; multiple treatments required; lack of safety and efficacy data
Crotamiton	10% ointment	Antipruritic and antibacterial activity; usually well tolerated	Infants	Yes	Multiple treatments necessary; efficacy questionable
Permethrin	5% cream	Effective	Infants, children, pregnancy; institutional settings	Yes	Previous sensitization against pyrethrins/neurotoxic adverse events; allergenic potential, may cause skin irritation; expensive
Ivermectin	Oral, 2×200 µg/kg 8-10 days apart	Effective; acts also against other ectoparasites and intestinal helminths	Resource-poor settings, institutional settings. Disseminated crusted scabies, patients with low immunocompetence;	Yes	Pregnant women, children <5 years/expensive; dose regimen has to be adjusted to infectious status

TOPICAL ACARICIDES

Based on the rationale that the mite is confined to the superficial layers of the epidermis, topical agents have been developed and used for decades. Initially, they held the promise of a high efficacy without the risk for adverse events. Problems associated with topical therapies, however, emerged rather soon after their introduction. The efficacy of the compounds varied from setting to setting and hints for the development of resistance became obvious.²

Topical therapies are laborious, require time-consuming applications, and some are even messy. The patient has to pay attention that the compound remains for the required time on his skin, must carefully wash off remaining cream or lotion, and eventually needs to apply a body cosmetic to counteract the irritating effect of the topical acaricide. Moreover, because *Sarcoptes* shares biochemical pathways with human⁴, and since most topical acaricides are actually pesticides with a neurotoxic mode of action, drug safety has become a matter of concern.⁵ In infants and small children the risk of toxic reactions is higher than in older individuals, because their body surface area is comparatively large and the scabicide may be licked off by the patient. As excoriations are common, the acaricide may penetrate into the blood circulation and cause systemic adverse events.

Various topical treatments are available. These include sulphur compounds which have been used for centuries; benzyl benzoate (first used in 1931); crotamiton (used

since the late 1970s); hexachlorocyclohexane, which is also known as gamma benzene hexachloride. The commercial purified form is lindane (available since 1948); malathion (used since the mid-1970s) and permethrin (in the USA first licensed in 1985).

Lindane

For more than 40 years, lindane has been the mainstay of therapy against scabies.

However, in only a few studies the efficacy of the substance has been assessed.

Amer et al.⁶ compared 1% topical lindane with 10% topical crotamiton and found a similar efficacy. In a study in Thailand, the efficacy of lindane was similar to that of 10% topical sulphur⁷. Five trials compared 1% topical lindane with 5% topical permethrin. The trials' combined estimate showed permethrin to be superior to lindane³. When compared with ivermectin, one study reported a similar efficacy and the other more treatment failures in the lindane group.^{8,9}

Serious adverse events may occur, particularly when the manufacturer's instructions are not followed rigorously. An application on altered skin or the use with a frequency greater than recommended, poses a health hazard to the patient.⁵ The danger of neurotoxic adverse events is particularly high in infants and young children.¹⁰ Toxic effects

include neurotoxic symptoms such as numbness, restlessness, anxiety, tremor and convulsions.¹¹ Accidental oral ingestion may lead to nervous system damage and death.⁵ Sudakin¹² reported a fatality after a single dermal application of lindane lotion. Oberoi et al.¹³ showed that the topical application of lindane causes oxidative stress in patients with scabies, as indicated by a significant increase in levels of malonaldehyde, superoxide dismutase and a decrease of blood glutathione.

Because of its potential neurotoxicity, lindane had always been contraindicated in infants, pregnant women, nursing mothers, and patients with seizures or other neurologic diseases. In the EU, lindane has been banned from use in agriculture since 2001 and from medical use in 2007. In 2002, California banned pharmaceutical use of lindane because of concerns about detrimental ecological consequences.¹⁴ Because of safety concerns and a rather low efficacy, lindane should no longer be used for the treatment of scabies.

Benzyl Benzoate

Benzyl benzoate was first known as a component of “balsam of Peru.” Hitherto, seven studies with an adequate study design are published. The concentration used varied between 10% and 25% and the efficacy between 48% and 91%.¹⁵⁻²¹ Benzyl benzoate performed similarly to topical sulphur in a study in India¹⁹ and to synergized natural pyrethrins in a study in Italy¹⁵. Three studies failed to observe a difference in cure rates after treatment with benzyl benzoate or oral ivermectin, whereas one study showed a superiority of ivermectin.^{16,18,20,21} Recently, in a study in the Senegal, benzyl benzoate was significantly more effective than a single dose of oral ivermectin (150-200 µg/kg).¹⁷ However, the dosage of ivermectin in the study was considered suboptimal.²²

Benzyl benzoate is a rapidly acting agent, but requires several applications, such as once to twice per day during 2 to 3 days; repeat after 10 days. Given its propensity to cause skin irritation, repeated applications should be performed with caution. The substance may produce a burning sensation, pruritus, and keratosis. The complicated regimen and the side effects reduce compliance. Mytton et al.²³ found no evidence of adverse events in pregnancy in a retrospective cohort study in Thailand.

Sulfur in Petrolatum

Sulfur in petrolatum has been used for centuries and it is still considered a first-line treatment in resource-poor settings. The substance needs to be applied for three consecutive nights and to be washed off thoroughly 24 hours after the last application.

Gulati 1978¹⁹ compared 25% topical sulphur ointment with topical benzyl benzoate. There was no difference between the two groups after 15 days. There was also

no difference between topical sulphur and 0.3% topical lindane.⁷

The substance is far from being cosmetically acceptable since it has a foul odor, it is messy and it stains clothing and bedding. It can also produce a toxic dermatitis. It had been considered safe, appropriate for infants younger than 2 months of age, and for pregnant women or lactating mothers.²⁴ However, Haustein²⁵ recently questioned the safety of the drug and considered its use obsolete in infants and small children because of its potential liver and kidney toxicity.

Crotamiton

Crotamiton (10% in a cream/lotion) is applied for 24 hours on 2 consecutive days. Since the compound is not very effective, some authors have suggested a 5-day application. In one study, crotamiton performed similar to 5% topical permethrin, in another study the compound was less effective.^{6,26}

The substance has an antipruritic effect but can induce an irritation of the skin and induce a contact dermatitis.^{27,28} Otherwise, crotamiton is considered safe for use in children and infants.

Malathion

There are still no published reports of randomized controlled trials that test the effectiveness of malathion against another drug, despite almost 30 years passing by since a noncontrolled study first suggested that the drug was effective. Malathion exists as a 0.5% alcoholic or aqueous solution. It is an organophosphate and inhibits the acetylcholinesterase irreversibly. The odour is quite objectionable, and inhaling the fumes can result in severe headaches.¹¹

Permethrin

Permethrin, a synthetic pyrethroid, is used in many countries as first line therapy. The recommended use is a single 10-hour application of a 5% cream. Hitherto, eight studies have assessed the efficacy of permethrin in comparison with other topical acaricides. When data of the different studies were combined in a meta-analysis, 5% topical permethrin was significantly more effective than 10% topical crotamiton or 1% lindane.³ Amerio et al.²⁹ compared 5% topical permethrin with 0.16% topical natural pyrethrins synergized with 1.65% pyperonil butoxide in a thermolabile foam. There were no treatment failures in either group after 28 days.

Permethrin is approved for use in infants >2 months of age. Mytton et al.²³ did not find any evidence of adverse effects of 4% permethrin on pregnancy.

Permethrin can cause a burning sensation, exanthema, pruritus and folliculitis.² Like other natural or synthetic

pyrethrins, permethrin has an allergic potential. Given its wide use in agriculture and gardening, previous sensitization of a child with scabies may have occurred. In this case, permethrin is contraindicated. Tomalik-Schäfer et al.³⁰ applied 5% permethrin cream to the skin of healthy adults and found that a substantial proportion of the substance is resorbed through intact skin. Presumably, in patients with scabies resorption is even higher because of the presence of multiple excoriations.

Since only low pyrethroid concentrations are necessary to modify sensory neurone function, neuromuscular adverse reactions may occur after a single application.³¹ The main adverse effect of dermal exposure is paraesthesia, presumably as a result of hyperactivity of cutaneous sensory nerve fibres. The face is affected most commonly and the paresthesiae are exacerbated by sensory stimulation such as heat, sunlight, scratching, sweating or the application of water.³¹ Coleman et al.³² reported a case of severe neck dystonia after topical application of 5% permethrin cream.

Natural pyrethrins applied in a thermolabile foam formulation seem to be better tolerated and reduced itching more rapidly than permethrin cream.²⁹

In other ectoparasites, such as head lice, permethrin resistance is widespread. This suggests that scabies mites may develop resistance, too. Anecdotal reports of failure in Australian remote communities may indicate emerging resistance.⁴ Furthermore, longitudinal studies conducted in northern Australia confirm increasing *in vitro* tolerance. In 1994, before widespread permethrin treatment was introduced, all mites were killed within 30 minutes of *in vitro* exposure to permethrin. By the year 2000, however, 35% of mites were alive after 3 hours of exposure and a significant proportion remained alive overnight. More recent analysis confirms increasing tolerance and shows that the permethrin is now the slowest acting acaricide *in vitro* in this region.⁴

HERBAL REMEDIES

Some essential oils kill sarcoptic mites. For example, tea tree (*Melaleuca alternifolia*) oil has been shown to be highly effective *in vitro*.³³ In an open clinical trial a paste composed of an extract of neem (*Azadirachta indica*) and of *Curcuma longa* (turmeric) cured 97% of patients with scabies.³⁴

Toto ointment and *Lippia multifolia* oil have been found to be useful in studies in Nigeria.^{35,36} Both treatments look promising, but randomized controlled trials making direct comparisons with the existing best treatments are needed to assess their true relative effectiveness and safety.

Ivermectin

The advent of ivermectin, a macrolytic lactone, has opened a new area in the treatment of scabies. Since the mid

1980s, ivermectin has been administered in humans, and until today several hundred million individuals have been treated with this drug in onchocerciasis and lymphatic filariasis control programs in Africa and South America. Owing to the possibility that the blood-brain barrier is incompletely developed in infants, raising the potential for ivermectin neurotoxicity, the drug is currently contraindicated in children less than 15 kg. It is also contraindicated in pregnant and lactating women. Despite these concerns, ivermectin has been used in large helminth control programs in these groups with no adverse effects, but because of a lack of comprehensive safety data, this barrier remains.⁴

In scabies studies, a single dose of ivermectin has been given. Based on the experience in endemic areas, we suggest two doses (200 µg/kg; repeat after 8–10 days). Comparative trials have shown that the efficacy is similar or better than that of topically applied lindane^{8,9} and is similar to that of benzyl benzoate.³ In a small study in India, Usha et al.³⁷ found more treatment failures in patients treated once with oral ivermectin compared to 5% topical permethrin. Alberici et al.³⁸ compared ivermectin and benzyl benzoate in HIV-associated crusted scabies. The investigators found that neither drug was effective when used in isolation and that combination therapy was the best option. Similarly, experience with crusted scabies patients in northern Australia strongly supports combination treatment, including multiple dose of ivermectin and topical acaricides.⁴ This indicates, that oral ivermectin may not replace topical substances entirely.

Ivermectin is considered to be a drug with an excellent safety profile.³⁹ Adverse events are rare, of minor importance and only of transient nature. At present, ivermectin is, except in a few countries such as in Mexico, Brasil, France, and the Netherlands, only approved for the treatment of helminth infections. However, off-label use on compassionate grounds for the treatment of simple and crusted scabies is common.⁴ If mass treatment is requested, such as during an epidemic, ivermectin is the drug of choice.⁴⁰

So far, resistance to oral ivermectin has been reported in two cases from Australia. These patients, aborigines with extremely severe crusted scabies, had received 30 to 58 doses of ivermectin over a period of 4 years.⁴¹

TREATMENT OF FOMITES

The treatment of clothing and bed linen (washing at 60°C, treatment with an antiscabietic lotion or putting it in a hermetically sealed bag for several days) is a frequent recommendation. However, this practice can be restricted to patients with multiple lesions or disseminated crusted scabies, since the risk of a reinfection through fomites seems to be low when the intensity of infestation is low.⁴²

TREATMENT FAILURE

Presumably, the majority of relapses are attributed to the lack of adherence to treatment protocols and a low compliance. Frequently, not all body parts are covered by the topical acaricide and particularly the head, the genitals or the periungual area are left untreated. In the case of treatment failure, a different compound should be used in order to avoid the development of resistance and/or cumulative toxicity. Resistance against neurotoxic acaricides is becoming a matter of concern and has been documented for crotamiton, lindane, and permethrin.⁴

CRUSTED SCABIES, IMMUNOCOMPROMISED PATIENTS

In crusted scabies, ivermectin is the drug of choice. Usually five to seven doses of oral ivermectin (200 µg/kg) have to be given. Some authors suggest a combination of ivermectin and topical permethrin.^{43,44} Ivermectin is also the drug of choice in scabies patients with innate or acquired immunodeficiency. Alberici et al.³⁸ suggest the combination of ivermectin and benzyl benzoate in HIV-associated crusted scabies.

Scabies in Children

The different treatment options currently in use are summarized in Table 30-2. As evidence is scarce, recommendations are based on reasonable best practice.

Scabies in Pregnancy

Due to safety concerns, how to treat scabies during pregnancy is a matter of debate (Table 30-2). Since ivermectin and lindane are contraindicated, only benzyl benzoate, crotamiton and permethrin remain as treatment options. Based on toxicologic considerations, Fölster-Holst et al.⁵ suggest the use of topical permethrin.

INSTITUTIONAL SETTINGS

The eradication of scabies epidemics in institutions requires careful planning and the collaboration between dermatologists, infections disease specialists, nurse staff, and the public health sector. Control is based on mass treatment of all residents irrespective of their infectious status, and should include the staff of the institutions and family contacts.⁴⁵ Mass treatment of the residents can be performed with oral ivermectin (two doses 200 µg/kg 1 week apart) or with 5% topical permethrin alone or in combination.^{46,47}

RESOURCE-POOR SETTINGS

In developing regions of the world, cost and availability of the acaricide are of obvious importance when selecting the most appropriate treatment for scabies. Ideally, the acaricide should be easy to apply, minimally absorbed through the skin, nontoxic for the host, and effective as a single-dose regimen. However, no drug currently fulfills all these criteria.

TABLE 30-2—Recommendations for Treatment of Scabies in Newborns, Infants and Children, During Pregnancy and Lactation^a

	Benzyl benzoate	Crotamiton	Permethrin	Malathion	Ivermectin
Newborn	Not recommended	Treatment only under strict medical supervision ^b	Treatment only under strict medical supervision ^b	Not recommended	Not recommended ^c
Infants	Treatment only under strict medical supervision ^b	Recommended ^d	Recommended ^d	Not recommended	Not recommended ^c
Children	Recommended ^e	Recommended ^d	Recommended ^d	Second line treatment ^f	Recommended
Pregnancy	Recommendation disputed ^g	Only in exceptional Cases	Treatment only under strict medical supervision	Not recommended	Not recommended ^h
Lactation	Treatment only under strict medical supervision ⁱ	Not recommended	Not recommended ^j	Not recommended	Not recommended ^h

^a Adapted from [2]

^b preferably in hospital setting

^c manufacturer does not recommend treatment in children less than 5 years or with less than 15 kg

^d only if skin is not excoriated or denuded; permethrin contraindicated if child is allergic against pyrethrins/pyrethroids

^e if child ≥ 6 years

^f an aqueous preparation should be used, because alcoholic preparations sting and cause wheeze

^g manufacturer allows prescription. In the USA, the prescription is prohibited as the embryo may develop a gasping syndrome⁵

^h by manufacturer. However, no adverse events were observed in thousands of women in inadvertently treated during pregnancy and lactation in helminth control programs

ⁱ do not apply on the breast and nipples

^j permethrin is present in breast milk

Because of its low cost, benzyl benzoate (10 to 25%) is commonly used in developing countries.

Mass treatment with ivermectin was successfully used to control scabies in resource-poor settings in Brazil and the Solomon Islands.^{40,48} In the latter study a single dose of ivermectin reduced prevalence from 25% to <1% for several months after intervention. Besides, the simultaneous elimination of the most common intestinal helminths, and of other ectoparasites by ivermectin is very much appreciated by polyparasitized patients typical in developing countries.

What We Know

- Scabies is an extremely itchy parasitic skin disease caused by the mite *Sarcopetes scabies var. hominis*. Transmission occurs mainly through direct contact from person to person. Fomites play only a minor role, except in disseminated crusted scabies.
- Scabies mimics many clinical conditions. The clinical manifestations depend on the age and the immunocompetence of the host.
- Treatment guidelines vary considerably between countries and are rarely based on evidence. Topically applicable compounds are sulfur in pretolatum, benzyl benzoate, crotamiton, permethrin, and malathion. Lindane should no more be used. All compounds require strict adherence to treatment protocols and some are potentially hazardous molecules. Resistance is emerging and is supposed to spread in the future. Oral ivermectin (200 µg/kg twice 8–10 days apart) is an excellent alternative and is the drug of choice in disseminated crusted scabies and in patients with altered immunocompetence.

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Treatment of Onychomycosis

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BACKGROUND

DEFINITION

Onychomycosis is a fungal infection of the nail caused predominantly by anthropophilic dermatophytes, less commonly by yeast (*Candida* spp.), and by nondermatophyte mold infections.^{1–3} Onychomycosis may present with hyperkeratosis, subungual debris, thickening, or discoloration of the nail plate. Total nail dystrophy may also result when onychomycosis is advanced.³

INCIDENCE/PREVALENCE

Onychomycosis is the most common nail disorder in adults. It accounts for approximately 50% of all nail diseases^{4,5} and has increased in individuals over the last 80 years.³ In North American centers, the prevalence of onychomycosis is between approximately 6.5% and 13.8%.^{4,6–8} Onychomycosis affects predominantly toenails compared to fingernails. In some reports the ratio of toenail to fingernail onychomycosis ranges from 4:1 to 19:1.^{4,7,9,10}

ETIOLOGY/RISK FACTORS

Predisposing factors for onychomycosis include tinea pedis, positive family history, increasing age, male gender, trauma, immunosuppression, diabetes mellitus, poor peripheral arterial circulation, and smoking.^{3,4,6,7,11–17} Additionally, for fingernails persistent exposure to water, the use of artificial nails, and trauma induced by pushing back the cuticles and aggressive manicuring are predisposing factors.

PROGNOSIS

Onychomycosis may be treated with systemic and/or topical antifungal agents, and most recently, devices have been used to treat onychomycosis. Traditional systemic agents used to treat onychomycosis include griseofulvin and ketoconazole. The newer oral agents used to treat onychomycosis are terbinafine, itraconazole, and fluconazole.^{18–25}

Recent data suggests that posaconazole may have efficacy. A recent randomized, placebo and active controlled, parallel, multicenter, blinded study not yet published in its entirety, studied treatment of patients with dermatophyte

DLSO (n=36-37 per regimen) with variable doses of posaconazole (100, 200, 400 mg/day for 24 weeks), as well posaconazole 400 mg/day and terbinafine 250 mg/day (both for 12 weeks duration).²⁶ The placebo arm of the study was treated for 24 weeks in keeping with the posaconazole dosing regimen arms. The primary efficacy endpoint of complete cure at 48 weeks was identified in 23%, 54%, 46%, 20%, 37%, and 0% for the posaconazole 100, 200, 400 mg/day (24 week regimen), 400 mg/day posaconazole (12 week regimen), 250 mg/day terbinafine, and placebo arms respectively. Of equal importance to efficacy, the frequency of adverse events did not differ significantly between treatment arms and were primarily mild in severity. As posaconazole is more efficacious and similar in safety at increased dosing compared to terbinafine 250 mg/day, its' use may become more mainstream.

Other azoles that have been reported to have some efficacy include ravuconazole.²⁷ Currently published data relating to the efficacy of another azole (voriconazole) as a drug to treat onychomycosis is limited to several manuscripts describing in-vitro studies.^{28,29}

Topical treatments include ciclopirox and amorolfine nail lacquers.^{30,31} Only ciclopirox nail lacquer 8% has been approved in the United States for the treatment of onychomycosis.³²

Relapse of onychomycosis, especially of toenails, is not uncommon, particularly in predisposed individuals. Reasons why fingernail onychomycosis responds better than toenail disease may be related to the fact that perfusion of the upper extremity is generally better than the lower extremity; this may result in improved drug delivery to the fingers compared to the toes. In addition, fingernails have a faster rate of outgrowth compared to toenails (3 mm/month compared to 1 mm/month),³³ resulting in the infected fingernail growing out faster than its lower extremity counterpart does.

AIMS OF TREATMENT

Onychomycosis may be a cosmetic problem, especially when fingernails are infected.³⁴ The treatment objectives are to reduce the fungal burden within the nail, ultimately curing the fungal infection, and to promote healthy regrowth of affected nails. In some instances, when onychomycosis is symptomatic, for example, pain, discomfort, soft tissue

infection, a timely treatment may help to eliminate symptoms and prevent complications that could be associated with more severe consequences.³⁵

RELEVANT OUTCOMES

The most commonly reported therapeutic measure of efficacy is mycologic cure, which is defined, by most, as negative light microscopic examination and negative culture. There are several ways by which clinical improvement has been reported. Some studies have used the parameter of clinical success, which is defined as cleared or markedly improved (90-100% clear nail).³⁶ Others have defined clinical success as cure or improvement sufficient to reduce the involved area of the target nail to less than 25% at the end of therapy.³⁷ Another term that has been used is clinical effectiveness, which is taken to be mycologic cure and at least 5 mm of new clear toenail growth.³⁸ Clinical cure refers to the post-therapy nail appearing completely cured to the naked eye. Complete cure rate is the combined results of mycologic and clinical cure.

METHODS

To identify studies where oral treatments, itraconazole (continuous and pulse), fluconazole, terbinafine (continuous and pulse) and griseofulvin were used to treat adults with toe- or fingernail onychomycosis caused by dermatophytes, we searched MEDLINE (1966-2010) for randomized-controlled trials (RCTs). The reference sections of the published reports were also examined for potential studies not listed in the database. Some of the studies were excluded for the following reasons:

Open trials, studies conducted in a special population (e.g., diabetics, Down syndrome, transplant patients), reports where we were unable to extract the relevant data, double publications, non-English language studies, and retrospective studies were excluded.

Onychomycosis caused by *Candida* spp. and nondermatophyte moulds is less common and the management of onychomycosis caused primarily by these organisms will not be considered in this chapter.

The use of most nail lacquers to treat onychomycosis will not be considered with the exception being ciclopirox discussed briefly herein. Although heralded as a safer alternative to systemic antifungal therapy, currently approved topicals for a large part have reported modest cure rates at best. For example, two pivotal studies and a collection of data from various European studies reported contradictory but modest complete cure rates of 5.5%, 8.5%, and 26.2% after 48 weeks of therapy in two North American and European studies, respectively.³² More recently, a novel water soluble formulation of ciclopirox in a solution containing hydroxypropyl chitosan has also been published with complete cure rate of ~ 13% assessed in 157 patients after 12 months of treatment followed up for a further 12 weeks after completion of therapy³⁹.

There are many anecdotal reports of various topical agents being effective for the management of onychomycosis; however, published reports of the efficacy of topical agents in onychomycosis in the indexed, peer-reviewed literature are far fewer. Other clinical trials have included tioconazole 28% solution, bifonazole with urea, fungoid tincture, miconazole, and tea tree oil.

This chapter discusses the distal and lateral presentation of dermatophyte onychomycosis, which is the most common type; the treatment of the other types of onychomycosis is not considered.^{3,40}

Also excluded were studies that used nonstandard treatment dosage or duration for toenails (e.g., terbinafine therapy <3 months or >4 months, itraconazole [continuous] therapy <3 months or >4 months, <200 mg/day, itraconazole [pulse] therapy <3 pulses or >4 pulses, fluconazole dosage other than 150 mg per week, griseofulvin therapy <3 months), fingernails (terbinafine therapy >6 weeks, itraconazole [continuous] therapy >6 weeks, itraconazole [pulse] >2 pulses, fluconazole dosage other than 150 mg per week), or other nonstandard regimens, such as sequential or combination therapy.

We have not considered trials where ketoconazole has been used to treat onychomycosis, given the potential of this agent to cause hepatotoxicity and the availability of alternative agents.

The use of posaconazole, ravuconazole, and voriconazole for the management of onychomycosis are not being discussed further in this chapter because the information currently available is limited.²⁶⁻²⁹

Several devices have been reported in the management of onychomycosis. This includes the use of laser systems, photodynamic therapy and iontophoresis. In many cases, the studies are in the form of case reports or open studies without adequate controls. In other instances the efficacy data, mycologic cure and clinical cure, and total cure 1 year from the start of treatment are not available in a published, peer-reviewed format.

Evidence was graded using the quality of evidence scale system employed by Cox et al.⁴¹

- I: Evidence obtained from at least one properly designed randomized control trial
- II- i: Evidence obtained from well-designed control trials without randomization
- II- ii: Evidence obtained from well-designed cohort or case control analytic studies, preferably from more than one center or research group
- II- iii: Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments could also be included
- III: Options of respected authorities based on clinical experience, descriptive studies, or reports of expert committees
- IV: Evidence inadequate owing to problems of methodology (e.g., sample size, length of comprehensiveness of follow-up or conflicts in evidence)

What is the role of oral antifungal therapy in the management of dermatophyte onychomycosis in adults?

Griseofulvin was the first significant oral antifungal agent available to manage dermatomycoses. Over the years the use of griseofulvin in the treatment of onychomycosis has decreased; although, it is still used for the treatment of tinea capitis, in countries where this agent is available.⁴² Ketoconazole, an oral imidazole, is no longer recommended for the treatment of onychomycosis, which requires a long duration of therapy, because of the potential for hepatotoxicity.⁴² The introduction of the new oral antifungal agents, terbinafine, itraconazole, and fluconazole has lead to improved efficacy rates, decreased treatment duration, and fewer adverse events.

QUESTION: What are the effects of systemic treatments on fingernail and on toenail onychomycosis?

OPTION: Griseofulvin

The regimen for treating onychomycosis is continuous therapy using a dosage of 500 mg/day to 1 g/day, typically administered for 6 to 12 months in fingernail onychomycosis and for 9 to 18 months in toenail disease.

Fingernail: Quality of Evidence – I

One randomized double-blind study compared griseofulvin to terbinafine in the treatment of onychomycosis (Table 31-1).⁴³

Fingernail: Effectiveness

In a double-blind randomized-controlled study(RCTs),⁴³ griseofulvin was given at a dosage of 500 mg/day for 12 weeks. The mycologic cure rate and complete cure rate was 63% and 39%, respectively.

Toenail: Quality of Evidence – I

Three double-blind RCTs^{44–46} and one open RCT⁴⁷ compared griseofulvin to terbinafine (continuous) or itraconazole (continuous) in the treatment of onychomycosis (Table 31-2).

Toenail: Effectiveness

In the RCTs, 500 mg/day or 1 g/day of griseofulvin was administered to treat onychomycosis. In the double-blind RCTs, the mycologic cure rate ranged from 45 to 69% and complete cure occurred in 2 to 56% of patients. In the open RCT, 6% of patients were completely cured.

TABLE 31-1—Treatment of Dermatophyte Fingernail Onychomycosis

Year	Author	Treatment	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (Post Treatment)	Efficacy Measure (%)		
								MC ^{†††}	CR [¶]	CC
2002	ITR Package Insert (US) ⁵⁴	ITRC	DB, R, Placebo-controlled	37	200 mg/day	2 mos		(61)	**	(47)
2001	TER Package Insert (US) ⁵⁵	TERC	DB, R, Placebo-controlled	Not Stated	250 mg/day	6 wks	24 wks	(79)	**	(59)
1997	Odom et al. ⁸⁷	ITRP	DB, R, Multi-center Placebo-controlled	37	400 mg / day 1 wk/mth	2 mos	Up to 19 wks	16/22 (73)	17/22 (77)	15/22 (68)
1998	Drake et al. ¹⁰⁵	FLUC	DB, R, Parallel, Multicenter, Placebo-controlled	78	150 mg/wk	Up to 9 mos	6 mos	70/78 (90)**	69/78 (88)	61/78 (78)**
1995	Haneke ⁴³	GRIS	DB, R, Comparative (TERC)	92	500 mg/day	12 wks, followed by 12 weeks placebo	6 mos	45/72 (63)		(39)

^{†††} Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;

[¶] MC defined as negative culture and a negative or missing microscopy result;

^{††} MC defined as negative microscopy;

^{¶¶} Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;

[†] CR variable definitions;

[‡] Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

^{**} Not defined; DB, double-blind; R, randomized; ITRP, itraconazole pulse; TERP, terbinafine continuous; FLUC, fluconazole.

TABLE 31-2—Treatment of Dermatophyte Toenail Onychomycosis Using Griseofulvin Therapy

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (Post Treatment)	Efficacy Measure (%)		
							MC ^{†††}	CR ^{††}	CC [‡]
1997	Baran et al. ⁴⁵	DB, R, Parallel, Multicenter, Comparative (TERC)	58	1 g/day	Up to 12 mos		(69)		(44)
1995	Faergemann et al. ⁴⁶	DB, R, Parallel, Comparative (TERC)	41	500 mg/day	13 mos		19/41 (46)**	**	1/41 (2) ‡‡
1995	Hofmann et al. ⁴⁴	DB, R, Comparative (TERC)	88	1000 mg/day	48 wks	24 wks	42/68 (62)	**	49/88 (56) ‡‡‡
1993	Korting et al. ⁴⁷	Open, R, Comparative (ITRC)	36	660 mg/day	Up to 18 mos		**	**	2/36 (6)
			36	990 mg/day			**	**	2/36 (6)

^{†††}Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;

^{††}Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;

[‡]CR variable definitions;

^{‡‡}Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

^{‡‡‡}CC defined as clinical cure and negative mycologic culture;

**CC defined as MC and continuous growth of unaffected nail;

** Not defined; DB, double-blind; R, randomized; ITRC, itraconazole continuous; TERC, terbinafine continuous.

Drawbacks

The use of griseofulvin may be associated with adverse events such as gastrointestinal upset, nausea, diarrhea, headache, central nervous system symptoms, and urticaria.⁴⁸ No drugs are contraindicated with griseofulvin and few drug interactions are associated with griseofulvin therapy.

Comments

Griseofulvin was the first systemic agent used to treat onychomycosis on a widespread basis. Currently, the newer oral agents (itraconazole, terbinafine, and fluconazole) have been found to be more effective than griseofulvin; the duration of active therapy is also shorter with the more recently introduced antimycotics.^{49,50} Moreover, when griseofulvin is used to treat dermatophyte, toenail onychomycosis relapse rates may be higher (40 to 60%)⁵¹ compared to the newer oral antifungal agents.^{35,52–55}

OPTION: Continuous Terbinafine

The regimen for fingernail and toenail onychomycosis is 250 mg/day administered for 6 and 12 weeks, respectively.

Fingernails: Quality of Evidence – I

Two double-blind, RCTs evaluated subjects with fingernail onychomycosis only (Table 31-1). One study administered

terbinafine for 12 weeks and therefore was not included in this analysis.⁴³

Fingernails: Effectiveness

The double-blind, randomized, placebo-controlled study used terbinafine 250 mg/day for 6 weeks to treat fingernail onychomycosis (Table 31-1).⁵⁵ Mycologic cure was achieved in 79% of patients and complete cure in 59%.

Toenails: Quality of Evidence – I

The majority of studies were double-blind RCTs (Table 31-3). Terbinafine was administered at a dose of 250 mg/day terbinafine for 3 to 4 months.

Toenails: Effectiveness

Six double-blind RCTs compared terbinafine to placebo.^{36,55–59} Each study reported terbinafine 250 mg/day to be significantly more effective than placebo in treating onychomycosis.

Fifteen double-blind, randomized studies compared terbinafine (continuous) to other drug comparators^{38,46,60–72} with mycologic cure rates ranging from 46 to 95% and the corresponding clinical response rates being 39 to 97%.

Four open RCTs reported the efficacy of terbinafine (continuous) for 3 or 4 months.^{73–76} Mycologic cure ranged

(text continues on page 424)

TABLE 31-3—Treatment of Dermatophyte Toenail Onychomycosis Using Terbinafine Continuous Therapy

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (From Baseline)	Efficacy Measure (%)		
							MC ^{¶¶¶}	CR ^{¶¶}	CC [#]
2009	Gupta et al ⁷²	Randomized, evaluator-blind, comparator-controlled (PT, PI)	32	250 mg/day	12 weeks plus booster 24 weeks later for 4 weeks identical treatment if necessary due to incomplete cure	18 months	78	66	Not reported
2006	Sigurgeirsson et al ⁷¹	Randomized, double blind, multi-center, double dummy, parallel, comparative (PT)	795	250 mg/day	12 weeks	12 months	74	47	42
2005	Shemer et al ⁷⁰	Randomized, comparative (-/+ ciclopirox)	34	250 mg/day	16 weeks	9 months	65	Not defined	50
			34	250 mg/day + ciclopirox	16 weeks + 9 months respectively	9 months	88	Not defined	68
2005	Gupta et al ⁶⁹	Randomized, evaluator blinded, comparative (pulse and +/- ciclopirox)	23	250 mg/day + ciclopirox	12 weeks and 12 months respectively	12 months	83	39	35
			21	250 mg/day	12 weeks	12 months	67	48	38
2005	Warshaw et al ⁶⁸	Randomized, double blind, comparative (TP)	148	250 mg/day	12 weeks	18 months	71	45	40
2002	Heikkila et al. ⁶⁰	DB, DD, R, Multicenter, Comparative (ITRP)	23	250 mg/day	12 weeks	72 weeks	Negative Microscopy: 21/23 (91) Negative Culture: 20/23 (87)	**	11/23 (48)**
			18		16 weeks		Negative Microscopy: 18/18 (100) Negative Culture: 17/18 (94)	**	9/18 (50)**

(Continued)

TABLE 31-3—Treatment of Dermatophyte Toenail Onychomycosis Using Terbinafine Continuous Therapy (Continued)

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (From Baseline)	Efficacy Measure (%)		
							MC [¶]	CR [¶]	CC [#]
2002	Sigurgeirsson et al. ⁶¹	DB, DD, R, Comparative (ITRP)	74	250 mg/day	12 or 16 weeks	Up to 5 years	34/74 (46)	**	26/74 (35)
2001	TER Package Insert (US) ⁵⁵	DB, R, Placebo-controlled	Not Stated	250 mg/day	12 weeks	48 weeks	(70)	**	(38)
2000	Havu et al. ⁶²	DB; Double-placebo, R, Multicenter, Comparative (FLUC)	46	250 mg/day	12 weeks	60 weeks	41/46 (89)	39/46 (85) ¹	**
1999	Evans et al. ³⁸	DB, DD, R, Parallel, Multicenter, Comparative (ITRP)	110	250 mg/day	12 weeks	72 weeks	81/107 (76)	67/102 (66) ¹	49/107 (46)
			99		16 weeks		80/99 (81)	67/95 (71)	54/98 (55)
1999	Degreef et al. ⁶⁵	DB, R, Parallel, Multicenter, Comparative (ITRC)	144	250 mg/day	12 weeks	48 months	(67)	(87)	**
1999	Billstein et al. ⁵⁷	DB, R, Parallel, Multicenter, Placebo-controlled	29	250 mg/day	12 weeks	72 weeks	18/21 (86)	**	**
			27		16 weeks		13/16 (81)	**	**
1998	De Backer et al. ⁶³	DB, R, Parallel, Multicenter, Comparative (ITRC)	186	250 mg/day	12 weeks	48 weeks	119/163 (73)	(76)**	(38)
1997	Drake et al. ³⁶	DB, R, Multi-center, Placebo-controlled	142	250 mg/day	12 weeks	48 weeks	(70)	58/71 (82)	**
1997	Svejgaard et al. ⁵⁸	DB, R, Multi-center Placebo-controlled	48	250 mg/day	3 months	9 or 12 months	19/48 (40)	**	18/48 (38)
1997	Honeyman et al. ⁶⁴	DB, DD, R, Parallel, Multicenter, Comparative (ITRC)	64	250 mg/day	4 months	48 weeks	61/64 (95) [¶]	62/64 (97)	61/64 (95)
1997	Tausch et al. ⁷⁸	DB, R, Multi-center, Duration finding	56	250 mg/day	12 weeks	48 weeks	46/56 (82)	33/56 (59) ¹	33/56 (59)

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (From Baseline)	Efficacy Measure (%)		
							MC ^{†††}	CR ^{††}	CC [‡]
1995	Brautigam et al. ⁶⁶	DB, R, Parallel, Multicenter, Comparative (ITRC)	86	250 mg/day	12 weeks	52 weeks	70/86 (81)	69/86 (80) **	**
1995	Faergemann et al. ⁴⁶	DB, R, Parallel, Comparative (GRIS)	43	250 mg/day	4 months		36/43 (84)**	**	18/43 (42)‡‡
1995	Watson et al. ⁵⁹	DB, R, Placebo-controlled	56	250 mg/day	12 weeks	24 weeks	33/56 (59)	**	
1994	De Backer et al. ⁶⁷	DB, R, Parallel, Comparative (TERC)	49	250 mg/day	4 months	48 weeks	41/49 (84)	44/49 (90)	**
			51	500 mg/day			46/51 (90)	45/51 (88)	**
1992	van der Schroeff ⁷⁷	DB, R, Duration-Finding	30	250 mg/day	6 weeks	48 weeks	12/29 (41)	**	12/30 (40)
			34		12 weeks		24/34 (71)	**	24/34 (71)
			34		24 weeks		28/34 (82)	**	27/34 (79)
1992	Goodfield et al. ⁵⁶	DB, R, Parallel, Multicenter, Placebo-controlled	45	250 mg/day	12 weeks	48 weeks	37/45 (82)	**	**
2002	Arca et al. ⁷³	Open, R, Comparative (ITRP, FLUC)	16	250 mg/day	3 months	6 months	12/16 (75)	**	10/16 (63)
1996	Alpsoy et al. ⁷⁵	Open, R Comparative (TERP)	24	250 mg/day	3 months	12 months	**	**	19/24 (79)
1999	Kejda ⁷⁶	Open, R, Parallel, Comparative (ITRP)	25	250 mg/day	3 months	12 months	(76)	17/25 (68)	**
1996	Tosti et al. ⁷⁴	Open, R Comparative (ITRP, TERP)	19	250 mg/day	4 months	10 months	16/17 (94)	**	13/17 (76)

^{†††}Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;

^{††}MC defined as negative microscopy;

^{††}Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;

[‡]CR variable definitions;

^{‡‡}Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

^{‡‡‡}CC defined as clinical cure and negative mycologic culture;

**Not defined; MIC, miconazole; DB, double-blind; DD, double-dummy; R, randomized; ITRP, itraconazole pulse; FLUC, fluconazole; ITRC, itraconazole continuous; GRIS, griseofulvin.

between 75 and 94%. In one study, clinical response was reported to be 68%.⁷⁶ Complete cure ranged between 63 and 79% for reported studies.

Two randomized double-blind studies investigated the optimal duration for terbinafine therapy^{77,78}. Mycologic cure assessed at 48 weeks was identified in 41%, 71-82%, and 82% after 6, 12, or 24 weeks of treatment, respectively. Similarly, 40%, 59-71%, and 79% of patients achieved complete cure after 6, 12, or 24 weeks of treatment, respectively, when assessed at 48 weeks. Clearly 12 weeks of therapy is more efficacious than 6 weeks, but by extending the therapy to 24 weeks little additional effect is gained.

Drawbacks

Treatment of onychomycosis with terbinafine (continuous) is associated with a low frequency of adverse events^{49,79}. These adverse events are generally mild to moderate in severity, and reversible. The more common adverse events involve the gastrointestinal tract, skin, and central nervous system. Terbinafine should not be used in individuals with systemic lupus erythematosus and Stevens-Johnson syndrome.⁵⁵ Only a small proportion of patients discontinue treatment with terbinafine. Few drug interactions have been reported, some of these may be explained by the allylamine inhibiting cytochrome P450 2D6.^{80,81} In the United States and Canada, the package inserts^{55,82} state that pretreatment serum transaminase tests (alanine transaminase and aspartate transaminase) should be considered before initiating terbinafine therapy.

Comments

Terbinafine is effective and safe for the treatment of onychomycosis. Terbinafine is an allylamine, which inhibits squalene epoxidase, resulting in an accumulation of squalene and a deficiency of ergosterol. The accumulation of squalene may be associated with fungicidal action.⁸³ In one study the relapse rate ($\geq 90\%$ clear nail at any time and <90% at last visit) was recorded in 15% of patients when followed up for up to 96 weeks from the start of therapy.³⁶ There are a substantial number of high-quality studies that demonstrate the effectiveness of terbinafine (continuous) in the treatment of toenail onychomycosis, some of which have stated that this may be the most effective agent available for this indication.^{84,85}

OPTION: Terbinafine (Pulse)

Terbinafine (pulse) is administered as 250 mg twice a day for 1 week on, followed by 3 weeks off between successive pulses. Typically, two pulses are required to treat fingernail onychomycosis and three or four pulses for toenail disease.

Toenails: Quality of Evidence – I

Seven studies have reported the use of intermittent terbinafine therapy in the treatment of onychomycosis (Table 31-4). Each of the studies is randomized and against a comparator; two are open^{74,75} and three are single-blind,^{69,72,86} and two are double-blind.^{68,71} The duration of follow-up is approximately between 10 to 18 months.

Toenails: Effectiveness

Five blinded, randomized studies^{68,69,71,72,86} compared terbinafine pulse to various therapeutics and regimens for administration. The mycologic cure rate in the pulse terbinafine groups varied from 47% to 84%, and complete cure rates were reported between 22% and 42%.

In the two open, randomized comparative studies^{74,75} intermittent terbinafine therapy was associated with complete cure rates of 50% (N=20)⁷⁴ and 74% (N=23).⁷⁵ Furthermore, in the study by Tosti et al.⁷⁴ the mycologic cure rate was 80%.

Drawbacks

Intermittent terbinafine therapy has been associated with few adverse events. Adverse events are generally mild to moderate, and reversible. The spectrum of adverse effects is similar to that seen with the continuous terbinafine regimen. Terbinafine (pulse) regimen is not indicated for the treatment of onychomycosis, and therefore there are no monitoring guidelines in the United States.

Comment

The preferred regimen for the treatment of onychomycosis using terbinafine is continuous rather than pulse therapy. Compared to the continuous regimen, which has been well-studied, there are relatively less data available on both the efficacy and safety of the pulse regimen. More robust studies are needed to determine the most effective regimen for terbinafine pulse therapy.

OPTION: Pulse itraconazole

Itraconazole pulse is taken to be 200 mg twice a day for 1 week on, followed by 3 weeks off between successive pulses. Typically, two pulses are administered for fingernail onychomycosis and three or four pulses for toenail disease.

Fingernails: Quality of Evidence – I

One double-blind, placebo-controlled trial investigated the efficacy of itraconazole (pulse) treatment in fingernail onychomycosis.

TABLE 31-4 — Treatment of Dermatophyte Toenail Onychomycosis Using Terbinafine Pulse Therapy

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (Post Treatment)	Efficacy Measure (%)		
							MC [¶]	CR	CC [‡]
2009	Gupta et al ⁷²	Randomized, evaluator-blind, comparator-controlled (TERC, PI)	43	250 mg/day for 4 weeks followed by 4 weeks rest	12 weeks plus booster 24 weeks later for 4 weeks identical treatment if necessary due to incomplete cure	18 months	84	79	Not Reported
2006	Sigurgeirsson et al ⁷¹	Randomized, double-blind, multicenter, double dummy, parallel, comparative (TERC)	796	350 mg/day for 2 weeks followed by 2 weeks rest	3 months	12 months	47	31	22
2005	Gupta et al ⁶⁹	Randomized, evaluator blinded, comparative (TERC and +/ - ciclopirox)	19	250 mg/day for one month and rest for 1 month + daily ciclopirox	4 months and 12 months respectively	12 months	74	47	42
2005	Warshaw et al ⁶⁸	Randomized, double-blind, comparative (TERC)	143	500 mg/day 1 wk/month	3 months	18 months	59	29	28
2001	Gupta et al. ⁸⁶	SB, R, Parallel, Comparative (ITRP+TERP)	90	500 mg/day 1 wk/month	3 months	18 months	44/90 (49)	41/90 (46) v	29/90 (32)
1996	Alpsoy et al. ⁷⁵	Open, R, Comparative (TERC)	23	500 mg/day 1 wk/mth	3 months	12 months	**	**	17/23 (74)
1996	Tosti et al. ⁷⁴	Open, R, Comparative (ITRP, TERC)	20	500 mg/day 1 wk/month	4 months	10 months	16/20 (80)	**	10/20 (50)

[¶] Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;

^{||}Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;

[‡]CR variable definitions;

^{*}Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

** Not defined; SB, single-blind, R, randomized; ITRP, itraconazole pulse; TERC, terbinafine continuous.

Fingernails: Effectiveness

In the double-blind, placebo controlled study the mycologic cure and clinical response rates were 73% and 77%, respectively (Table 31-1).⁸⁷

Toenails: Quality of Evidence – I

Ten RCTs, five of which were double-blind and five open, evaluated itraconazole pulse in the treatment of toenail

onychomycosis (Table 31-5). Two further comparator studies investigated the efficacy of pulse itraconazole compared to other antifungal drugs, or differing dosing regimens (Table 31-5). More recently, in a study not yet published in its' entirety, the effectiveness of a 200 mg tablet has been evaluated. In a RCT, one group of patients received itraconazole 200 mg in tablet form with a daily dose of 400 mg per day for 1 week with 3 weeks off between successive pulses, for three pulses. The comparator group received itraconazole 100 mg capsules, the dosage being 200 mg

TABLE 31-5—Treatment of Dermatophyte Toenail Onychomycosis Using Itraconazole Pulse Therapy

Year	Reference	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up Period (From Baseline)	Efficacy Measure (%)	MC ^{LL}	CR ¹¹	CC ¹²
2009	Gupta et al ⁷²	Randomized, evaluator-blind, comparator-controlled (PT, TERC)	30	400 mg/day 1 wk/mth followed by 1 week of 400 mg/day after 3 months	12 weeks plus booster 24 weeks later for 4 weeks identical treatment if necessary due to incomplete cure	18 months	57	37	Not Reported	Not Reported
2006	Shemer et al ⁹³	Comparator (PI regimens)	43	400 mg/day 1 wk/mth followed by 1 week of 400 mg/day after 3 months	13 weeks	12 and 24 months	68 (12), 60 (24)	Not Reported	Not Reported	Not Reported
			40	400 mg/day 1 wk every 6 weeks followed by 1 week of 400 mg/day after 3 months	13 weeks	12 and 24 months	74 (12), 63 (24)	Not Reported	Not Reported	Not Reported
2002	Heikkila et al. ⁶⁰	DB, DD, R, Multicenter, Comparative (TERC)	18	400 mg/day 1 wk/mth	12 wks	72 wks	Negative Microscopy: 11/18 (61) Negative Culture: 12/18 (67)	6/18 (33)**	**	3/17 (18)**
			17			16 wks	Negative Microscopy: 11/17 (65) Negative Culture: 13/17 (76)			
2002	Sigurgeirsson et al. ⁶¹	DB, DD, R, Comparative (TERC)	77	400 mg/day 1 wk/month	12 or 16 wks	Up to 5 years	10/77 (13)	**	11/77 (14)	
2000	Gupta et al. ⁸⁹	DB, R, Placebo-controlled	78	400 mg/day 1 wk/month	3 months	48 wks	48/78 (62)	51/78 (65)	**	

1999	Evans et al. ³⁸	DB, DD, R, Parallel, Multicenter, Comparative (TERC)	107	400 mg/day 1 wk/month	12 wks	72 wks	41/107 (38) 53/108 (49)	29/102 (28) ¹ 35/104 (34) ¹	25/107 (23) 28/108 (26)
1997	Havu et al. ⁹⁰	DB, R, Parallel, Multicenter, Comparative (TERC)	59	400 mg/day 1 wk/month	3 months	12 months	41/59 (69)	48/59 (81)	**
2002	Arca et al. ⁷³	Open, R, Comparative (TERC, FLUC)	18	400 mg/day 1 wk/month	3 months	6 months	11/18 (61)	**	11/18 (61)
1999	Shemer et al. ⁹¹	Open, R, Comparative (ITRC)	Minimum of 16 patients in each group	400 mg/day 1 wk/month	3 months	48 wks	**	**	(50)
1999	Kedja ⁷⁶	Open, R, Parallel, Comparative (TERC)		400 mg/day 1 wk/month	3 months	12 months	(75)	20/26 (77)	**
1996	Tosti et al. ⁷⁴	Open, R, Comparative (TERC, TERP)	21	400 mg/day 1 wk/month	4 months	10 months	15/20 (75)	**	8/21 (38)
1996	De Doncker et al. ⁹²	Open, R, Comparative (ITRP)	25	400 mg/day 1 wk/month	3 months	Up to 1 yr	16/25 (64)	22/25 (88)	**
			25		4 months	4 months	18/25 (72)	21/25 (84)	**

^{1,2,3}Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;¹Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;²CR variable definitions;³Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise; ITRC, terbinafine continuous; ITRC, terbinafine randomized; R, randomized; DB, double-blind; DD, double-dummy.⁴Not defined; DB, double-blind; DD, double-dummy; R, randomized; TERC, terbinafine continuous; FLUC, fluconazole.

twice a day for 1 week pulse, with 3 weeks off between successive pulses.⁸⁸

Toenails: Effectiveness

One double-blind RCT compared three pulses of itraconazole to placebo.⁸⁹ A significant difference was present between the mycologic cure rate of itraconazole (62%) and placebo ($P<0.0001$). A significant difference also existed between the clinical response rate in the active treatment (65%) compared to the placebo group ($P<0.001$).

Four double-blind, randomized comparative studies evaluated itraconazole pulse treatment, three compared to continuous terbinafine treatment,^{8,60,61} and one compared to continuous itraconazole treatment.⁹⁰ The mycologic cure rates for the itraconazole pulse groups ranged between 13 and 69%. The corresponding range for clinical response rates were between 28 and 81%.

Five open, randomized comparative studies^{73,74,76,91,92} reported mycologic cure rates of itraconazole that ranged between 61 and 75%, and clinical response rates between 77 and 88%.

More recently, two comparator studies administering slight variations on the standard 400 mg/day itraconazole pulse regimen of 1 week per month for approximately 3 months duration reported mycologic cure rates between 57% and 74% in keeping with data from previous studies^{72,93}.

Drawbacks

Itraconazole (pulse) therapy is approved for fingernail, but not toenail, onychomycosis in the United States. Adverse events occur with a low frequency and are generally mild to moderate in severity, and reversible. These events include gastrointestinal upset, cutaneous eruption, and headache.⁹⁴ Studies report a low discontinuation rate as a result of an adverse event. Itraconazole can have an interaction with several drugs.^{54,80,71,95} There are several drugs that are contraindicated with itraconazole.^{50,92} In some cases the drug interaction may be explained on the basis of an inhibition of cytochrome P450 3A4 by itraconazole. Itraconazole is contraindicated in North America (USA and Canada) in patients with evidence of ventricular dysfunction, for example, congestive heart failure or a history of heart failure.^{54,96} Hepatic enzyme test values should be monitored in patients with pre-existing hepatic function abnormalities or those who have experienced liver toxicity with other medications. Hepatic enzyme test values should be monitored periodically in all patients receiving continuous treatment for more than 1 month, or at any time a patient develops signs or symptoms suggestive of liver dysfunction.^{54,96}

Comments

Itraconazole pulse therapy is effective and safe in onychomycosis. The pulse regimen used to treat toenail

onychomycosis decreases the itraconazole required by one-half compared to the continuous regimen with this triazole. This may result in monetary saving, increased compliance, and possibly reduce the frequency of adverse events.^{89,94,97-99} In fact, the pulse regimen is the preferred mode of drug delivery when using itraconazole. No significant difference was found between 3 and 4 pulse regimens of itraconazole for the primary efficacy parameters in the treatment of toenail onychomycosis.⁹² In one report, after the use of three pulses for the treatment of toenail onychomycosis, the relapse rate at follow-up, 12 months after the start of therapy, was 10.4%.⁹⁹ Two pulses of itraconazole should be effective and safe in fingernail onychomycosis. Itraconazole pulse therapy is not approved in the United States for the management of toenail onychomycosis, although it may be used off label in that manner to treat dermatophyte toenail onychomycosis.

OPTION: Continuous itraconazole

The regimen for fingernail and toenail onychomycosis is 200 mg/day administered for 6 and 12 weeks, respectively.

Fingernails: Quality of Evidence – I

One double-blind, randomized study compared itraconazole (continuous) with placebo in the treatment of fingernails only⁵⁰ (Table 31-1).

Fingernails: Effectiveness

The double-blind RCTs used a continuous regimen of itraconazole to treat fingernail onychomycosis.⁵⁴ The mycologic cure rate was 61% and the corresponding complete cure rate was 47%.

Toenails: Quality of Evidence – I

The majority of reported studies were double-blind RCTs (Table 31-6).

Toenails: Effectiveness

In the five double-blind RCTs that compared itraconazole (continuous) with placebo, significantly more patients receiving active treatment achieved mycologic cure and clinical response ($P<0.01$).^{54,100-102} The mycologic cure rates for the RCTs treating patients with itraconazole continuous ranged from 46 to 84%; the corresponding range for clinical response rates was 58 and 83%.

Seven miscellaneous comparative trials employed arms that studied the efficacy of continuous itraconazole therapy in treating dermatophyte onychomycosis and produced mycologic cure or complete cure rates varying between 46-84% or 23-76% respectively^{63-66,90,91,103}

TABLE 31-6 — Treatment of Dermatophyte Toenail Onychomycosis Using Itraconazole Continuous Therapy

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up Period (From Baseline)	Efficacy Measure (%)		
							MC ^{†††}	CR ^{††}	CC [‡]
2002	ITR Package Insert (US) ⁵⁴	DB, R, Placebo-controlled	110	200 mg/day	12 wks		(54)	**	(14)
1999	Degreef et al. ⁶⁵	DB, R, Parallel, Multicenter, Comparative (TERC)	145	200 mg/day	12 wks	48 wks	(61)	(82)	**
1998	Haneke et al. ¹⁰³	DB, R, Parallel, Multicenter, Comparative (ITRC + ITRP, MIC)	479	200 mg/day	3 months	12 months	354/479 (74)	395/479 (82)	**
1998	De Backer et al. ⁶³	DB, R, Parallel, Multicenter, Comparative (TERC)	186	200 mg/day	12 weeks	48 weeks	77/168 (46)	(58)**	(23)**
1997	Elewski et al. ¹⁰⁰	DB, R, Multicenter, Placebo-controlled	109	200 mg/day	12 weeks	48 weeks	59/109 (54)	71/109 (65)	
1997	Havu et al. ⁹⁰	DB, R, Multicenter, Parallel, Comparative (ITRP)	62	200 mg/day	3 months	12 months	41/62 (66)	43/62 (69)	**
1997	Honeyman et al. ⁶⁴	DB, DD, R, Parallel, Multicenter, Comparative (TERC)	70	200 mg/day	4 months	12 months	59/70 (84) ^{††}	58/70 (83) [†]	53/70 (76)
1995	Brautigam et al. ⁶⁶	DB, R, Parallel, Multicenter, Comparative (TERC)	84	200 mg/day	12 weeks	52 weeks	53/84 (63)	63/84 (75)**	**
1996	Jones et al. ¹⁰¹	DB, R, Placebo-controlled	35	200 mg/day	12 weeks		24/35 (69) **	27/35 (77)**	18/35 (51)**
1996	Odom et al. ¹⁰²	DB, R, Placebo-controlled	38	200 mg/day	12 weeks	48 weeks	18/38 (47)	26/38 (68)	14/38 (37)
1999	Shemer et al. ⁹¹	Open, R, Comparative (ITRP)	Minimum of 16 patients in each group	200 mg/day	3 months 4 months	48 weeks	** **	** **	(68) (65)

^{†††} Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;^{††} MC defined as negative microscopy;[†]Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;[‡]CR variable definitions;[‡]Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

** Not defined; MIC, miconazole; DB, double-blind; R, randomized; ITRP, itraconazole pulse; TERC, terbinafine continuous.

Recently, a novel formulation of itraconazole was developed and evaluated in a randomized, placebo-controlled, multicenter, parallel group, evaluator-blinded study; however, it has yet to be published in its' entirety.⁸⁸ This data from this study compared complete cure at 52 weeks in evaluable patients to dermatophyte DLSO treated for 12 weeks with itraconazole daily in either 1 × 200 mg formulation (n=496), 2 × 100 mg formulation (n=517), and placebo (n=156). Complete cure was achieved in 22.3%, 21.7%, and 1% of the 200 mg formulation, 100 mg formulation and placebo arms of the study, respectively⁸⁸.

Drawbacks

Adverse events associated with the use of continuous itraconazole for the treatment of onychomycosis are not common, and those experienced are generally mild to moderate in severity. Adverse events include gastrointestinal disorders (e.g., nausea, abdominal pain), rashes, and central nervous system effects (e.g., headache).^{90,94,97-99} Only a small proportion of patients discontinue treatment with the triazole. There are drugs that are contraindicated with itraconazole (see section on itraconazole pulse therapy above). In addition, the triazole has several drug interactions (see section above). Itraconazole is contraindicated in North America in patients with evidence of ventricular dysfunction, for example, congestive heart failure or a history of heart failure. The U.S. package insert suggests that liver function tests be performed in patients receiving continuous therapy for more than 1 month or at any time a patient develops signs and symptoms suggestive of liver disease.⁵⁴

Comments

Continuous itraconazole therapy is an effective and well-tolerated treatment of onychomycosis. Historically, treatment of onychomycosis with itraconazole was with the continuous regimen; later, work done by de Doncker et al.^{92,99} resulted in the widespread adaptation of pulse therapy for this indication. In the U.S. package insert, when patients with toenail onychomycosis were treated with itraconazole continuous therapy, 21% of the overall success group had a relapse (worsening of the global score or conversion of KOH or culture from negative to positive).⁵⁴

OPTION: Fluconazole

The treatment regimen of fluconazole for onychomycosis is 150 mg once weekly administered until the affected nail has grown out. Typically, the duration of therapy for fingernail and toenail disease has been 4 to 9 months and 9 to 15 months, respectively.¹⁰⁴

Fingernail: Quality of Evidence – I

One double-blind RCT assessed the efficacy of fluconazole in the treatment of fingernail onychomycosis (Table 31-1).

Fingernail: Effectiveness

The randomized, double-blind study¹⁰⁵ compared various regimens of fluconazole to each other and with placebo in the treatment of fingernail onychomycosis. Fluconazole 150 mg/week administered for up to 9 months, resulted in a mycologic cure rate of 90% and a clinical response rate of 88%.¹⁰⁵

Toenails: Quality of Evidence – I

Few double-blind RCTs have been reported.^{37,62} (Table 31-7).

Toenail: Effectiveness

In the double-blind RCTs^{37,62} mycologic cure ranged between 49 to 53%. The corresponding clinical response rates were 23 to 77%. In the open RCT, 31% of patients were mycologically cured.⁷³

Drawbacks

Fluconazole is not approved for the treatment of onychomycosis in North America. The more common adverse effects observed with fluconazole affect the gastrointestinal, cutaneous system, and central nervous system.^{81,104} Adverse events do not commonly occur, and those experienced are usually of mild to moderate severity, and reversible. Only a small proportion of patients discontinue treatment with fluconazole. The drugs contraindicated with fluconazole are cisapride and terfenadine. There are some drug interactions that may occur with the triazole; in certain cases, the drug interactions may be explained by fluconazole inhibiting cytochrome P450 2C9 and at higher doses the triazole may inhibit cytochrome P450 3A4.^{80,81}

Comments

Fluconazole is effective and safe in onychomycosis. Compared to terbinafine and itraconazole, there are relatively few studies that have evaluated the efficacy of fluconazole in the treatment of toenail onychomycosis. The preferred regimen for fluconazole is once weekly therapy; typically 150 mg per week administered for several months until the abnormal-appearing nail plate has grown out. In the study reported by Scher et al.³⁷ the clinical relapse rate over a 6 month follow-up was 4.4%.⁵² Studies evaluating the use of once weekly fluconazole at a higher dosage such as 300 mg or 450 once weekly,^{37,105} or continuous fluconazole

TABLE 31-7—Treatment of Dermatophyte Toenail Onychomycosis Using Fluconazole Therapy

Year	Author	Study Type	Number of Evaluable Patients	Regimen	Treatment Duration	Follow-Up (Post Treatment)	Efficacy Measure (%)		
							MC ^{¶¶¶}	CR ^{¶¶}	CC [#]
2000	Havu et al. ⁶²	DB, Double-placebo, R, Multicenter, Comparative (TERC)	43	150 mg/week	12 weeks	60 weeks	22/43 (51)	10/43 (23) [¶]	**
			41		24 weeks		20/41 (49)	18/41 (44) [¶]	**
1998	Scher et al. ³⁷	DB, R, Parallel, Multicenter, Placebo-controlled	73	150 mg/week	Up to 12 months	6 months (only those Pts that were clinically cured or improved)	38/72 (53)	56/73 (77)	**
2002	Arca et al. ⁷³	Open, R, Comparative (ITRP, TERC)	16	150 mg/week	3 months	6 months	5/16 (31)	**	5/16 (31)

^{¶¶¶}Mycologic cure (MC) defined as negative microscopy and culture unless indicated otherwise;

^{¶¶}Clinical Response (CR) defined as cured or markedly improved unless indicated otherwise;

[¶]CR variable definitions;

[#]Complete Cure (CC) defined as mycologic and clinical cure or improvement unless indicated otherwise;

^{**}Not defined; MIC, miconazole; DB, double-blind; R, randomized; ITRP, itraconazole pulse; TERC, terbinafine continuous.

administration have not been discussed. It would be beneficial to have robust data on the relative efficacy of fluconazole 150 mg once weekly compared with 300 mg once weekly and 450 mg once weekly.

GENERAL COMMENTS

There have been several pharmacoeconomic analyses of the various oral treatments used in dermatophyte onychomycosis. These studies calculate the cost-effectiveness of each therapy based on the efficacy results of multiple clinical trials. The two most cost-effective regimens for the treatment of onychomycosis are terbinafine (continuous) and itraconazole (pulse).^{81,106–110} In the United States both terbinafine and itraconazole are available in generic formulations. Thus, the cost of these agents is not as much of an issue in the United States compared to the pregeneric era.

In certain nail presentations response to therapy may be improved by combining oral antifungal therapy with either an effective topical therapy or mechanical/chemical measures (e.g., mechanical avulsion, debridement, or chemical avulsion). For example, when there is lateral onychomycosis, a dermatophytoma, severe onycholysis, a thickened nail, or severe onychomycosis, it may be advantageous to consider a combination approach.^{111–116}

THERAPEUTIC DEVICES

Device-based therapy for onychomycosis is presently being developed in two manners. The first involves a device to

either deliver drug (iontophoresis), or in conjunction with a drug (photodynamic therapy). The second class of device for treating onychomycosis does not involve coadministration of drug but rather utilizes the device alone to provide therapy (lasers).

Iontophoresis

This type of device-based therapy utilizes a charged drug molecule, which is passed into and through the nail plate by means of a mild electric current in order to achieve greatly enhanced drug concentrations at the site of the infection. This is an improvement upon topical drug therapy (passive diffusion of drug) by substantially increasing the drug concentrations at the site of infection. Furthermore, the increased drug concentrations are achieved without an increased risk of adverse events such as are frequently encountered during systemic therapy.

Although several studies have been published using in-vitro models to test the efficacy of iontophoresis to deliver drug through a nail plate experimentally, only one study has carried out in-vivo work on onychomycosis patients. In this study patients were treated with 1% terbinafine HCL administered either actively by iontophoresis or passively through diffusion overnight, 5 days per week for 4 weeks and assessed 1 week later. Due to the short duration of the study, and the corresponding slow growth rate of the great toenail being treated, commonly measured efficacy rates were not feasibly studied. Instead, two parameters of efficacy were monitored: (1) clinical

improvement (outgrowth of ≥ 1.5 mm of new nail) and (2) mycologic improvement (reduced numbers of elements in the nail specimen). For clinical improvement, the percent of patients with ≥ 1.5 mm of clear nail growth treated by iontophoresis was 42% versus 18% of patients treated without iontophoresis. Similarly, after treatment with iontophoresis, significant improvement was seen as assessed by mycologic examination because 15% of patients tested had fungal elements in their nail specimens compared to 53% in those not treated with iontophoresis¹¹⁷.

Photodynamic Therapy (PDT)

PDT involves the use of visible light to activate drug in a lacquer format once applied and sufficient time has elapsed for the drug to penetrate the nail plate to the site of infection. As previously outlined in relation to iontophoresis, most studies to date involve in-vivo examination of drug efficacy using PDT.

However, one case report describes chemical avulsion of a patient's nail followed by drug administration and PDT activation with treatment being repeated twice at 15-day intervals. Mycology samples were positive after the third treatment, however, converted to negative 3 months later and were still negative when tested at a 12 months follow-up visit¹¹⁸.

Lasers

Lasers as a source of light are routinely used in medical procedures currently and are steadily increasing in their applications. Recently lasers as a device have begun to be studied as a means of providing non-drug related treatment for onychomycosis. However, despite a modest number of manuscripts having studied this from an in-vitro perspective, little or no firm data exists as to the mechanism of action involved in this therapy. Despite this fact, studies have been undertaken in-vivo to examine the efficacy of lasers in treating onychomycosis.

The first study by Bornstein et al. studied a small ($n=7$) number of patients with various fungal infections including *Trichophyton* species. Patients were treated with a laser using a dual wavelength exposure (870 nm/930 nm) for 4 minutes followed by single wavelength exposure (930 nm) for a further 2 minutes with a 1.5 cm spot size on days 1, 7, 14, and 60. During treatment, nail temperature was monitored and a physiologic temperature was maintained ($\leq 38^{\circ}\text{C}$) at the site, and by day 60, all patients had negative mycology test results¹¹⁹.

A second study of the efficacy of laser therapy on treating onychomycosis from Bornstein et al. performed a randomized-controlled study.¹²⁰ As with the previous study, patient population was not homogeneous in terms of clinical and mycologic presentation. In this study patients

What We Know

- The main oral antifungal agents used to treat onychomycosis are terbinafine, itraconazole, and fluconazole. Griseofulvin and ketoconazole are the traditional anti-fungal agents whose utility for onychomycosis has decreased substantially since the availability of the new oral antifungal agents. In addition, the use of ketoconazole for onychomycosis has diminished markedly given the potential for hepatotoxicity.
- The preferred regimens with the new oral antifungal agents are terbinafine (continuous), itraconazole (pulse), and fluconazole (once weekly). The duration of therapy with these agents for fingernail onychomycosis is typically: terbinafine continuous (6 weeks), itraconazole pulse (2 pulses), and fluconazole once weekly (6 to 9 months). The corresponding duration of therapy with these antifungal agents for toenail onychomycosis is 12 or 16 weeks, 3 or 4 pulses, and 9 to 15 months, respectively.
- RCTs have demonstrated that griseofulvin, terbinafine (continuous), itraconazole (pulse and continuous), and fluconazole are effective and safe for treatment of dermatophyte fingernail onychomycosis.
- RCTs have demonstrated that terbinafine (continuous), itraconazole (pulse and continuous), and fluconazole

are effective and safe for treatment of dermatophyte toenail onychomycosis.

- There are early studies looking at the role of devices such as laser therapy, and the combination of drugs and devices, for example, photodynamic therapy and iontophoresis. The published data available from these studies are often from open studies or small trials, thereby making it difficult to critically evaluate the place of these treatment modalities in the management of onychomycosis.
- There are several factors that need to be considered when deciding which agent to prescribe for onychomycosis; these include, efficacy, causative organism, regimen preference (e.g., continuous vs. pulse versus once weekly, expected duration of therapy), safety of antifungal agent, medical status of patient, potential for drug interactions, relapse rates, and cost of therapy.
- The efficacy of antifungal agents in the management of onychomycosis caused by *Candida* species and nondermatophyte molds is outside the scope of this chapter.
- None of the newer oral antifungal agents has been approved for the treatment of onychomycosis in children, where the disease occurs much less frequently.

(n=44) were treated on days 1, 14, 42, and 120 with treatment parameters identical to the previously described study.¹¹⁵ In the control arm, sham treatment (n=15) with no energy output was administered. After the final treatment, patients were followed out to day 180, however negative fungal culture was observed to be maximal on day 60 (75% of patients treated), and negative microscopy peaked on day 120 (64% of patients treated). At day 180, mycologic cure was observed in 30% of the patients treated. This data was not presented for the sham-treated patients.

In order that a comparison of efficacy can be performed between the oral agents, topical treatments, and devices (with or without a drug combination), it is important that the efficacy criteria remain the same, that is complete cure rate (complete clinical cure with mycologic cure [simultaneously negative light microscopy and culture]). Additionally, to best assess the efficacy of lasers to treat dermatophyte DLSO compared to drugs or the other class of devices, it is imperative that future studies be performed in a manner, whereby screening of patients is performed to assess the organisms involved and the extent of the disease present, rather than treating "all comers" which constitutes a homogeneous patient population.

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Treatment of Leprosy (Hansen's Disease)

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INTRODUCTION

Leprosy, also known as Hansen's Disease, is caused by a chronic granulomatous immune response to infection of the skin, upper respiratory tract, eyes, nerves, and testes, with the acid fast bacteria *Mycobacterium leprae* and the recently described closely related bacteria *Mycobacterium lepromatosis*.¹ About 5% of the population in endemic areas is susceptible to infection, and recent studies have revealed a range of human lymphocyte antigen-D (HLA-D) related immune responses to the organism.

The diversity of clinical and histopathological host responses depends on the ability of the host to develop a cellular immune response to *M. leprae*.² Patients with relative good cell mediated immunity and a delayed type IV hypersensitivity reaction to *M. leprae* present with few well-demarcated hypoesthetic skin lesions. These individuals have tuberculoid leprosy (TT) and develop well-formed granulomas with few if any acid-fast bacilli in tissue. At the other end of the spectrum are individuals with no

immunity to *M. leprae*. They present with numerous skin lesions, have sheets of macrophages containing many bacilli on histology, and have lepromatous leprosy (LL). (Figure 32-1) The majority of patients fall in between these two polar forms of leprosy and have fluctuations in their immunity to the bacilli. Those who are immunologically closer to tuberculoid disease have borderline tuberculoid leprosy (BT) (Figure 32-2) and those closer to lepromatous disease have borderline lepromatous leprosy (BL). (Figure 32-3) Patients who have an absence of bacilli on skin-slit smear or biopsy are classified by the World Health Organization (WHO) as paucibacillary disease (PB) and those who have the presence of bacilli are multibacillary (MB). The WHO clinically classifies patients with five or less than five lesions as PB and those with more than five lesions as MB (Table 32-1).

A primary neuritic leprosy exists when no skin lesions are present but the patients have nerve damage³ (Figure 32-4). Histoid leprosy is a form of lepromatous leprosy in which the cutaneous lesions are firm, well-demarcated

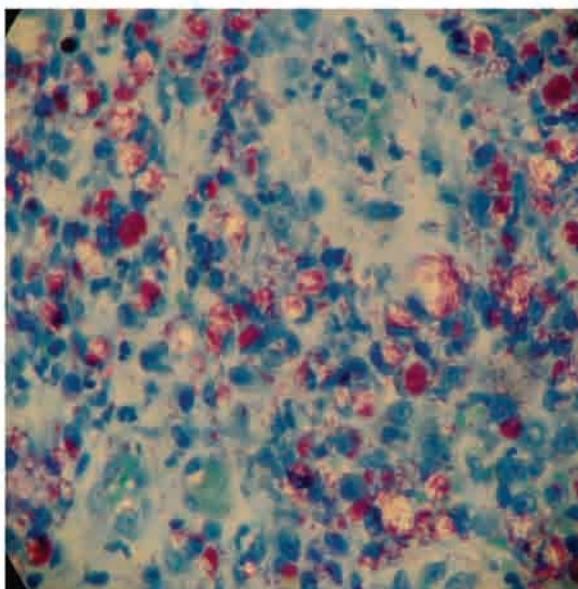


FIGURE 32-1 Histology of a lesional skin biopsy from a lepromatous leprosy case with Fite-Faraco modification of the carbol fuchsin stain showing acid-fast bacilli singly and in clumps (globi) within macrophages. (100x magnification)



FIGURE 32-2 A Tibetan patient with borderline tuberculoid leprosy who has well demarcated erythematous hypopigmented and anesthetic patches in an asymmetric distribution overlying the upper trunk.

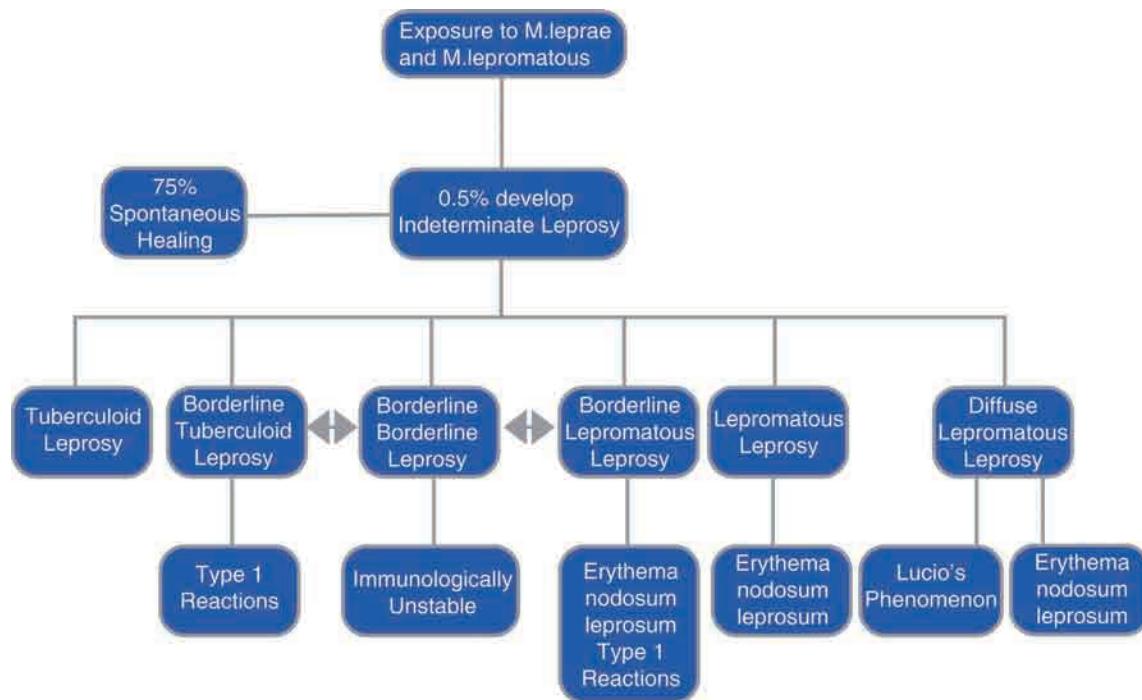


FIGURE 32-3 (A) Borderline lepromatous leprosy. This patient has madarosis, alopecia of the eyelashes, and bilateral ulnar nerve paralysis that has resulted in the claw hand deformity. (B) Borderline lepromatous leprosy consists of symmetrically located erythematous annular plaques with characteristic feathering of the edges and partial central clearing.

nodules reminiscent of dermatofibromas (Figure 32-5). Diffuse lepromatous leprosy may present with erythema nodosum leprosum and neuropathy without clinical evidence of skin lesions. Indeterminate leprosy is the earliest form of Hansen's disease and 75% of these individuals have an immunity that spontaneously clears the infection (Figure 32-6).

The WHO estimates that worldwide 2-3 million people live with physical disabilities secondary to leprosy.⁴ Neural damage results from the infectious granulomas created by *M. leprae* and by hypersensitivity reactions to the viable or dead bacilli. Early recognition and treatment of leprosy and its reactions is critical to reduce the degree of permanent neurological damage in these patients.

TABLE 32-1—Ridley-Jopling Classification Scheme



Ridley-Jopling Classification Scheme and the immunologic reactions, which are associated with the various forms of leprosy. The borderline category is immunologically unstable (double arrows) and these individuals can undergo upgrading of their immune status and move towards the tuberculoid pole, whereas a decrease in delayed hypersensitivity will cause a shift towards the lepromatous end of the spectrum.



FIGURE 32-4 Tenosynovitis of both dorsal hands in a patient with pure neural leprosy. There were no skin lesions but when biopsied demonstrated presence of bacilli, and also had arthralgias of the hands and decreased skin sensation of the hands and elbows.

EPIDEMIOLOGY

In 2009, the WHO reported the global registered prevalence of leprosy to be 213,036.⁴ The number of new cases detected in 2008 was 249,007.⁴ At this time the WHO reports that the number of new cases annually has remained relatively constant over the last 5 years with a decline of 3.54% per year since 2007. The majority of new cases were reported from India, Brazil, and Indonesia. About 3000 cases of relapse are reported worldwide annually after completing multidrug therapy (MDT). Some of these cases are felt to be due to under treatment of MB that has been misdiagnosed as PD.

MB patients may shed up to several million bacilli daily in their nasal secretions; hence, the nose is believed to be the major portal of exit.⁵ It is thus believed that the most likely portal of entry for the leprosy bacillus is the respiratory tract. There are some reports of transmission via penetrating wounds through intact skin, such as by thorns, fomites, and tattoos.⁶ Phenolic glycolipids (PGL-1), a component of the electron transparent zone of the cell envelope of *M. leprae*, have been isolated from soil and soil



FIGURE 32-6 Indeterminate leprosy in a patient who had emigrated from a leprosy endemic region. This patient had one well-circumscribed erythematous plaque on the face that was associated with decreased sensation. A biopsy revealed a granulomatous infiltrate surrounding adnexal structures and cutaneous nerves.

may also be a source of infection.² Untreated multibacillary patients represent the major source of infection and chemotherapy renders the nasal discharge bacteriologically negative within several days. Humans are the major host and reservoir for *M. leprae*. Natural infections are also reported in wild armadillos in Texas, Louisiana, and Brazil, as well as in chimpanzees and Mangabey monkeys. In adults, men are twice as likely to contract infection with *M. leprae*, and reactions are generally more common in men. In women, lepromatous reactions are seen more frequently during the third trimester of pregnancy and the post-partum period. The incidence of conjugal leprosy is around 5%.⁷

Children and infants are more susceptible to leprosy than adults are, and children are an indicator of the prevalence of the disease in the general population. Up to 60% of children will develop evidence of disease upon exposure to infectious family members in endemic areas and 75% have a positive Fluorescent Leprosy Antibody Absorption Technique (FLA-ABS).⁸ The average incubation period is 2-7 years and the peak incidence is between 5 to 9 years of age. Up to 20% of children born to mothers with leprosy in endemic areas will develop the disease by puberty. In endemic regions, most children will present with tuberculoid or



FIGURE 32-5 (A) Histoid leprosy, a form of lepromatous leprosy, consists of firm, fixed, shiny nodules that are most numerous on the face and extremities. (B) The cutaneous lesions in histoid leprosy often present with a central umbilication.

indeterminate skin lesions (70%). Fortunately, the majority of cases of early leprosy in children are self-healing. Two thirds of children with HD will have neural involvement, yet reactional states in children are less frequently reported than in adult populations. Due to the long incubation period, leprosy is most often diagnosed in adults, at which time the patients may already have significant disabilities. Leprosy in children under one year of age is rare but has been reported, the youngest being 2-3 months old, and 57% of infants have a history of contact with an infected individual, the mother being the most common source.⁹

Household contacts of patients with PB disease have a two-fold increased risk for developing HD and household contacts of MB disease have a 5 to 8-fold risk of the disease. Up to 30% of household contacts may develop the disease and there is a predilection for males and younger individuals.¹⁰ Since treatment has become more available, advanced cases of lepromatous leprosy are rare. Ulcerative ENL, amyloidosis, nephrotic syndrome and death are uncommon complications following implementation of MDT by the WHO.^{2,5}

Pregnancy, in the absence of treatment, is generally associated with worsening disease.⁷ However, reversal reactions are more common in the puerperium and erythema nodosum leprosum (ENL) occurs more frequently in the third trimester and following parturition. Both types of reactions can reoccur throughout lactation. Fifty six percent of women experienced immunologic flaring of their disease during their third trimester, 50% developed Type 1 lepra reactions during the first six months of lactation, and 68% developed Type 2 lepra reactions during the third trimester and the first six months of lactation. The leprosy reactions are caused by fluctuations in cell mediated and humoral immunity secondary to hormonal changes and women with HD require close supervision with frequent follow-up visits during pregnancy and lactation. There is decreased placental size, intrauterine growth retardation, delayed growth and development, and an increased risk for infections and mortality in infants born to mothers with leprosy, and these findings were more severe in mothers with LL.

DIAGNOSIS

The clinical picture of Leprosy is comprised of skin manifestations and ocular and peripheral nerve damage. Skin lesions consist of hypopigmented patches, papules, and plaques overlying the cooler parts of the body such as the face, ears, and extremities. The cutaneous lesions generally have reduced sensation to light touch. Nerve damage commonly follows a pattern of mononeuritis multiplex, presenting with sensory and motor deficits as well as autonomic dysfunction. The patients have peripheral numbness or anesthesia, paresthesia, dysesthesia or allodynia, muscle weakness or paralysis, and anhydrosis, cutis laxa, and alopecia.¹¹ Alopecia is due to the destruction of follicles by

the leprous granulomatous process. A characteristic presentation is the loss of the lateral eyebrows (Figure 32-7a), called madarosis. Epistaxis is common secondary to involvement of the nasal mucosa, which may progress to destruction of the nasal bone; the sinuses may also be involved. Granulomatous infiltration of the oropharynx presents with hoarseness (Figure 32-7b).

In tuberculoid leprosy the patients present with one or a few isolated well-demarcated infiltrated anesthetic patches; these are sometimes associated with a palpable proximal superficial nerve.⁵⁻⁷ In BT the patches are more numerous, but still well demarcated and tend to be distributed asymmetrically (Figure 32-2). BL has more widespread and more symmetrical skin lesions, which may or may not have associated anesthesia. The cutaneous lesions have less well-defined borders and are less anesthetic. (Figure 32-3a and 3b) LL results in diffusely infiltrated skin, which subsequently presents as shiny papules or plaques. These lesions favor the cooler parts of the body, where the density of bacilli is greater. (Figure 32-7a-7d) The early skin lesions do not have decreased sensation but do so later in the disease. Combined large nerve involvement, such as the ulnar and median and the common peroneal and posterior tibial, create the glove and stocking anesthesia of hands and feet. In some cases of LL the skin is diffusely infiltrated without evident skin lesions, and the first presenting sign of HD may be neuropathy or ENL.

There are no serologic tests or skin tests (other than histology) with the sensitivity and specificity to allow for routine use in the clinical setting to diagnose Hansen's disease. To make a diagnosis of leprosy, one must have at least one of the following: skin lesions with an abnormal sensory perception, enlarged peripheral nerves, and/or the presence of acid fast bacilli in skin biopsy or peripheral skin smears.¹² The presence of all three cardinal signs has a sensitivity of 97% and a positive predictive value of 98%.

Although sensory impairment is easily detected in skin lesions, 30% of cutaneous lesions in MB do not have associated anesthesia. There is also considerable variation in clinician's abilities to detect enlarged peripheral nerves, which may occur in other diseases such as neurofibromatosis, entrapment neuropathies, and genetic sensorimotor neuropathies.¹³ Slit skin smear examination, although highly specific, have a low sensitivity secondary to sampling error from the skin sites selected for testing.¹⁴ The slit skin smear examination can be used to quantify the number of acid-fast bacilli in infected skin lesions as well as to follow patients before and after treatment. The reliability of this test is dependent on the ability of the clinician to perform and inspect the histology of the slit skin smear.

In PB disease, where bacilli may be difficult to find on histology, polymerase chain reaction analysis may be performed on tissue sections to assist in the detection of *M. leprae*. Serologic testing for PGL-1 antibodies may also be helpful in supporting the diagnosis of lepromatous leprosy, but neither test is approved in the United States for routine clinical use.¹⁵



FIGURE 32-7 (A) Lepromatous leprosy. Diffuse infiltrated plaques on the ears, nose, eyebrows, cheeks and chin with associated Clofazimine hyperpigmentation. There are leonine faces, madarosis, and large pendulous ears. (B) Lepromatous leprosy patient who presented with hoarseness secondary to involvement of the oropharynx, here the infiltrated palate lesions are accentuated by Clofazimine hyperpigmentation. (C) Lepromatous Leprosy showing typical diffusely and symmetrically distributed shiny nodules over the back with relative sparing over the spine. (D) Patient with a long history of untreated lepromatous leprosy, stocking-glove anesthesia, and mitten hand deformity.

A full thickness skin biopsy from the edge of a skin lesion is still the “gold standard” to diagnose leprosy. The tissue is fixed in neutral buffered formalin and embedded in paraffin. Histological sections are stained with hematoxylin and eosin to identify the host response and the Fite-Faraco modification of the carbol fuchsin stain or Gomori methenamine silver stain to identify acid-fast bacilli in dermis and nerves^{2,16} (Figure 32-1).

CLASSIFICATION OF LEPROSY

The clinical, pathological, and immunological features of Hansen's disease present with a wide range of clinical and pathological manifestations. In 1873, Dr. Gerhard Henrik Armauer Hansen (1841-1912), a Norwegian physician, discovered that the causative agent of leprosy was *M. leprae*. Until the time of his discovery, leprosy was thought to be hereditary or a disease imposed on individuals as a curse from god, and those afflicted suffered discrimination and persecution.¹⁷

There are two classifications of leprosy: the Ridley-Jopling scheme and the WHO classification. The Ridley-Jopling

scheme classifies leprosy on a scale from tuberculoid to lepromatous leprosy. The WHO classification consists of paucibacillary disease and multibacillary disease² (Table 32-2).

William Jopling (1911-1997), a leprologist at the Jordon Leprosy Hospital in England, together with D. S. Ridley, a pathologist, proposed a classification of leprosy taking into account the Lepromin reaction of the patient and the number of *M. leprae* bacilli in tissue (Table 32-3).¹⁸ The Lepromin skin test was developed by Dr. Kenuke Mitsuda in 1919 and involves a subcutaneous injection of a standardized extract of inactivated leprosy bacillus.¹⁹ The injection site is examined 3 and 28 days after injection. The Fernandez reaction occurs 24-48 hours after injection and represents a type IV delayed type hypersensitivity reaction to soluble leprosy antigens. The Mitsuda reaction occurs about 21 days after injection, reflecting cell mediated immunity and is represented by a cutaneous granuloma 4 mm or greater in diameter. A positive Lepromin test is seen in individuals able to mount a strong immune response to one of the antigens found in the leprosy bacilli (human, athymic mice, or armadillo derived).¹⁹ A positive Mitsuda reaction may also be seen in the majority

TABLE 32-2—Summary of the Immunologic Responses and Treatments Used for Leprosy

Ridley-Jopling Classification	Indeterminate Leprosy	Tuberculoid Leprosy	Borderline Tuberculoid Leprosy	Borderline and Mid-Borderline Leprosy	Borderline Lepromatous Leprosy	Lepromatous Leprosy
Clinical Classification	One skin lesion with decreased sensation	One to three asymmetrically located well demarcated patches and plaques with xerosis, decreased sensation, and alopecia	More numerous skin lesions and less well demarcated than in TT, asymmetric enlargement of peripheral nerves	Numerous skin lesions, often with a targetoid appearance (erythematous edges with a pale center), skin lesions more or less symmetrically located, multiple peripheral nerve trunks involved	Numerous symmetrically located macules and papules, symmetrical involvement of nerve trunks, lesions often have preserved sensation	Widespread involvement of skin and other organs, shiny nodules and plaques symmetrically distributed with coarsening of facial features (Leoneine facies) and loss of lateral eyebrows (madarosis), nasomaxillary and laryngeal involvement, ocular keratitis and iritis
Mitsuda Skin Reaction	- / - + / +	+++ / ++++	++ / ++	- / +	- / +	-
Burden of Bacilli in Tissue	- / (+)	- / +	- / +	++	+++	++++
NHDP Treatment	<ul style="list-style-type: none"> - Rifampicin 600 mg once - Ofloxacin 400 mg once - Minocycline 100 mg once (ROM) 	<ul style="list-style-type: none"> - Dapsone 100 mg daily × 2 years (children 1-2 mg/kg) - Rifampicin 300 mg daily × 2 years (children 10 mg/kg) - Clofazimine 50 mg daily × 2 years (children 1-2 mg/kg) 				
Cytokine profile	Type 1 reactions - IL-2, IFN-γ, TNF (stimulates macrophage activity)			Type 2 reactions - IL-4, IL-5, IL-10, IL-13 (suppresses macrophage activity)		
Host Immunity	Th1 CD4+ T-cell response - cell mediated immunity - Type IV hypersensitivity reaction			Th2 CD4+ T-cell response - Antibody response - Immune complex formation - Neutrophilic dermatosis (Sweet's like) - Erythema nodosum leprosum		
Reactions	None	Rare RR	RR	RR / ENL	RR / ENL	ENL
WHO MDT	<ul style="list-style-type: none"> - Rifampicin 600 mg once - Ofloxacin 400 mg once - Minocycline 100 mg once (ROM) 	<ul style="list-style-type: none"> - Dapsone 100 mg daily × 6 months (children 1-2 mg/kg) - Rifampicin 600 mg once per month supervised × 2 years (children 10 mg/kg) - Clofazimine 300 mg once per month supervised and 50 mg daily × 2 years (children 1-2 mg/kg for both monthly and daily doses) - If Clofazimine pigmentation is objectionable, it may be replaced by daily ethionamide or prothionamide 				
Slit Skin Smear, number of bacilli	-	- / +		+ (bacillary index equal to or greater than 2)		
WHO-clinical classification	One skin lesion with decreased sensation	Less than 6 skin lesions with sensory disturbance		Six or more skin lesions		
WHO Classification	Indeterminate	Paucibacillary		Multibacillary		

Summary of the immunologic responses and treatments used for leprosy. The Ridley-Jopling Scheme is at the top of the chart with the corresponding clinical findings seen in the different forms of leprosy.^{11,18} At the bottom of the chart is the corresponding classification used by the World Health Organization (WHO).² The host immunity ranges from a strong cell-mediated response to *M. leprae* at the left side of the chart to no immunity at the right of the chart. The National Hansen's Disease Program (NHDP) differs from the Multi Drug Therapy (MDT) program recommended by the WHO. The NHDP is longer, with two drugs administered daily for one year for Tuberculoid Leprosy (TL) and triple therapy daily for two years in both borderline disease and Lepromatous Leprosy (LL). The WHO organization administers one monthly-supervised dose of Rifampicin to reduce the cost of treatment. PB disease is treated with two drugs for 6 months and MB disease is treated with three drugs for two years. PB disease is associated with a strong Th1 CD4+ T-cell response and reversal reactions (RR).^{35,36} MB disease, on the other hand, has a predominantly Th2 CD4+ T-cell response and is associated with RR and Erythema nodosum leprosum (ENL).^{6,7,35,48} Indeterminate leprosy is treated with a single dose of Rifampicin, Ofloxacin, and Minocycline (ROM). The bacillary burden in tissue increases on both histology and slit skin smear as the host immunity decreases.^{12,16} The Mitsuda skin reaction is more pronounced in the setting of a good cell mediated immunity of *M. leprae*.^{18,19}

of people from non-endemic areas and in contactants to patients with leprosy, as well as in patients with tuberculoid leprosy. Negative reactions are seen in lepromatous leprosy and weakly positive reactions are seen in the borderline spectrum of HD (Table 32-2).

For diagnosis of leprosy in endemic countries, where there is a risk for transmission of other infectious diseases such as Human Immunodeficiency Virus (HIV) and Hepatitis B from unsanitary surgical instruments used for skin biopsies and slit skin smears, as well in the field lack of equipment to read and personnel capable of interpreting the results, the WHO has decided to train medical personnel to classify leprosy by counting the number of skin lesions instead of performing invasive procedures. For practical reasons, the WHO has redefined the classification of HD as follows: a single hypopigmented lesion Indeterminate Leprosy, 1-5 skin lesions Paucibacillary Disease (PBD), and more than five skin lesions as Multibacillary disease (MBD).²

MICROBIOLOGY

M. leprae is an acid-fast staining, microaerophilic, nonmotile, non-spore forming, obligate intracellular curved or straight bacterium that grows and divides inside Schwann cells and macrophages. It favors temperatures around 27-30°C and has an estimated in vivo replication time of every 12-14 days. It is weakly acid fast and appears as red rods when stained with the Fite Faraco method.²⁰ The cell wall consists of chains of alternating N-acetylglucosamine and N-glycolylmuramate linked by peptide cross-bridges. These in turn are linked to a galactan layer by arabinoglycan and the galactan layer is linked to three branched chains of arabinan, making up the electron-dense zone surrounding *M. leprae*.²¹ Arabinan is linked to galactan and forms the inner leaflet of the pseudolipid bilayer. The outer leaflet, also called the electron-transparent zone, is composed of mycolic acids, mycoserosic acids, trehalose monomycolic acid, phthiocerol dimycocerosaic acid, and phenolic glycolipids (PGL-1).

The primary lipid in the bacterial cell wall is PGL-1 and interacts with laminin of Schwann cells, resulting in inflammation and nerve damage.²² *M. leprae* has never been grown in artificial medium and is propagated in animal models; mice (normal, euthymic and gene knockout) and the nine banded armadillo (*Dasypus novemcinctus*) for research purposes and for testing drug resistance of the bacillus.^{23,24} The mouse footpad model is an in vivo system that allows research on *M. leprae* by inoculating a suspension containing the bacilli into the footpads of BALB/C and CBA mice. After 6 months a biopsy obtained from the inoculated tissue is evaluated to characterize the host-parasite relationship of leprosy. This animal model has been also used to determine viability of *M. leprae* organisms, to test for drug effectiveness and resistance, and to develop new forms of chemotherapy.²⁴ The MDT for leprosy was developed with information derived from the mouse footpad system. The armadillo is a natural host for *M. leprae*, and with its lower

body temperature, the bacilli replicate readily and large numbers of organisms can be isolated for biochemical and immunologic research such as vaccine development and investigation of the leprous neuritis.²³

TREATMENT OF LEPROSY

From as early as 600 B.C., through the writings of Sushtra from India, there is evidence of Hydnocarpus Oil being used to treat leprosy and an Egyptian physician is reported to have used the oil back in ancient times. Until the 1940s, Chaulmoogra oil had been the treatment for leprosy. It was relatively ineffective and caused significant injection site reactions.²⁵ In 1943, based on reports that promin was successful in the treatment of *Mycobacterium tuberculosis*, Guy Henry Faget and coworkers treated several Hansen's patients in Carville, Louisiana with promin resulting in regression of skin lesions and cures. Until this time there had been no effective treatment and this success was called "The Miracle at Carville" and published in the book with the same title by Betty Martin. In 1946 and 1947, Robert Cochrane (in an injected formulation) and John Lowe (in an oral formulation) respectively, used a related drug called Dapsone to treat HD and found it to be better tolerated than promin. Dapsone became widely used for the treatment of leprosy in the 1950s, yet it is only bacteriostatic, and in time this monotherapy resulted in the development of Dapsone-resistant bacilli.²⁶

It became essential to develop new and more powerful drugs to treat leprosy. This led to the development of Clofazimine, a dye, which is mainly bacteriostatic and mildly bactericidal as well as anti-inflammatory, and was first used by Stanley G. Browne to treat HD. In 1962, Clofazimine was added to Dapsone to treat lepromatous patients. In the early 1970s, Rifampicin emerged as the first bactericidal drug to treat leprosy, and in 1982 the WHO recommended a MDT regimen using all three drugs to treat and cure all MB disease patients² (Tables 32-3 and 32-4).

TABLE 32-3—Ridley's Logarithmic Scale

Ridley's Logarithmic Scale	Bacillary Burden per 100 magnification of the Histologic Field
6+	>1000 bacilli in an average field
5+	100-1000 bacilli in an average field
4+	1-100 bacilli in an average field
3+	1-10 in an average field
2+	1-10 in 10 fields
1+	1-10 in 100 fields
0	No bacilli seen after screening 200 fields

Ridley's Logarithmic Scale used in the Ridley-Jopling classification scheme.¹⁸ The numbers of bacilli are quantified in skin specimens, and the numbers increase logarithmically with decreasing cell-mediated immunity. Following treatment of leprosy with MDT, the cell wall remnants are cleared slowly by the immune system; approximately half to one log per year. This explains why LL patients may continue with ENL up to 10 years after completion of treatment.⁴⁸

TABLE 32-4—Summary of Commonly Used Medications in the Treatment of Leprosy and its Reactions⁷⁰

Drug	Dose	Mechanism of action	Laboratory Monitoring	Side effects
Non-reactive disease therapy				
Dapsone	100 mg daily	- Bacteriostatic - Inhibits bacterial synthesis of dihydrofolate reductase - Anti inflammatory: inhibits myeloperoxidase	- Check for G-6-PD deficiency - Complete Blood Count - Liver Function Tests	- Dapsone Hypersensitivity syndrome - Toxic hepatitis - Methemoglobinemia - Hemolytic anemia - Agranulocytosis
Rifampicin	300 mg daily	- Bactericidal - Inhibits bacterial RNA-polymerase	- Liver function tests	- Hepatotoxicity - Flu like symptoms - Orange discoloration of body fluids
Clofazimine	50 mg daily	- Binds bacterial guanine bases - Inhibits macrophages and neutrophil mobility	- Liver Function Tests	- Brown-purple skin pigmentation - Accumulation of crystalline Clofazimine in lymph tissue (may lead to intestinal obstruction) - ichthyosis
Floxacillin	400 mg daily	- Bactericidal - Inhibits DNA-gyrase	- Liver Function Tests	- Spontaneous tendon rupture - Hepatitis - Peripheral neuropathy - Psychiatric disturbances
Minocycline	100 mg daily	- Bactericidal: binds 30S ribosomal subunit - Anti-inflammatory: inhibits 5-lipoxygenase - Apoptosis	- Liver Function Tests	- Vertigo - Dizziness - Autoimmune hepatitis - Drug induced lupus - Pseudotumor cerebri - Expired medication is nephrotoxic - Blue-grey pigmentation of the skin and mucous membranes
Clarithromycin	dose: 500 mg daily	- Bactericidal: binds 50S ribosomal subunit	-Liver Function Tests	- Dizziness - Creatinine - Diarrhea - Caution in patients with QT prolongation or taking Buspirone
Reaction therapy				
Thalidomide	100-300 mg daily	- Inhibits TNF- α	- Pregnancy test in females	- Teratogenic-contraindicated in pregnancy - Increases risk for thromboembolism - Peripheral neuropathy
Prednisone	10-80 mg daily	- Immunosuppressant	- Blood glucose - With long term use consider bone density testing and - <i>Pneumocystis carinii</i> prophylaxis	- Adrenal suppression and Cushingoid features - Increases risk for diabetes and osteoporosis - Insomnia - Osteoporosis - Glaucoma
Colchicine	dose: 0.6 -1.2 mg daily	- Anti-inflammatory - Binds tubulin - Inhibits mitosis - Inhibits neutrophil motility and activity	- Complete Blood Count	- Contraindicated in renal failure - Bone marrow suppression - Diarrhea
Pentoxifylline	400-800 mg three times daily	- Anti-inflammatory - Inhibits TNF- α and leukotriene	- None	- Gastrointestinal upset
Azathioprine	50-150 mg daily	- Inhibits purine synthesis	- Complete Blood count - Alkaline Phosphatase	- Bone marrow suppression - Increased opportunistic infections - Increased risk of malignancies

	Dose	Mechanism of action	Laboratory Monitoring	Side effects
Methotrexate	10-20 mg weekly	- Antimetabolite - Inhibits dihydrofolate reductase - Add folate supplementation to reduce risk for toxicity	- Complete Blood Count - Liver Function Tests - Pregnancy test in females	- Teratogenic, contraindicated in pregnancy and in men trying to get their partner pregnant - Hepatotoxic - Contraindicated in renal disease
Cyclosporine	300 mg daily	- Calcineurin inhibitor - Inhibits interleukin-2	- Complete Blood Count - Renal Function Tests - Liver Function Tests - Blood pressure	- Nephrotoxic - Hepatotoxic - Hyperplasia of the gingiva - Increased opportunistic infections and malignancies
Acedapsone	225 mg intramuscular injection daily	- Bacteriostatic: Prodrug of Dapsone	- Check for G-6-PD deficiency - Complete Blood Count - Liver Function Tests	- Dapsone Hypersensitivity syndrome - Toxic hepatitis - Methemoglobinemia - Hemolytic anemia - Agranulocytosis
Ethionamide	250 mg twice daily	- Bactericidal - Inhibits synthesis of mycolic acid	- Liver Function Tests - Thyroid Function Tests - Blood Glucose	- Gastrointestinal intolerance - Depression - Neuritis, reduced by coadministration of pyridoxine - Hepatitis - Hypoglycemia - Teratogenic
Prothionamide	500 mg daily	- Bactericidal - Inhibits synthesis of mycolic acid	- Liver Function Tests - Thyroid Function Tests - Blood Glucose	- Hepatotoxic, increased risk when administered with Rifampicin - Hypothyroidism - Hypoglycemia - Peripheral and optic neuropathy - Metallic taste - Depression
Etanercept	50 mg injected twice weekly	- Inhibits TNF- α	- Liver Function Tests - Rule out infection with tuberculosis and hepatitis B	- Increased risk of infections - Contraindicated in tuberculosis and hepatitis B infection

Summary of commonly used medications in the treatment of leprosy and its reactions.⁷⁰ The mechanisms of action, appropriate laboratory monitoring, and most common side effects are described.

IMMUNOLOGY, VACCINES, AND CHEMOPROPHYLAXIS

The host immunity determines the clinical manifestation of infection with *M. leprae*. A robust Th-1 type cytokine production is seen in TT and a suboptimal pro-inflammatory response with predominate Th-2 type cytokines is seen in lepromatous leprosy. HLA studies in a southern Brazilian population revealed that HLA-DRB1*1601 was associated with susceptibility to borderline leprosy, HLA-DRB1*08 was associated with susceptibility to lepromatous leprosy, and HLA-DRB1*04 was associated with resistance to infection.²⁷

The role of vaccines in leprosy is to induce a cellular immunity and to induce the differentiation of memory CD8+ cytotoxic T cells.^{28,29} The Bacillus Calmette–Guérin (BCG) vaccine, initially developed to induce protection against tuberculosis (TB), was found to convey some protection

against leprosy, but its effectiveness varies, depending on the report. A past meta-analysis did not provide evidence of its efficacy due to the heterogeneity of the methods and results, yet a more recent meta-analysis revealed that there might be some efficacy when controlled for the age at the time of vaccination, the clinical form of leprosy, as well as the number of doses administered. Genetic variations in the BCG vaccine strain and genetic variations in test subjects also lead to variable efficacy.²⁸ Isolated studies reported from the Indian experience using the BCG-Galaxo, BCG-Japan, and BCG-French-Danish vaccine strains, revealed a protective effect in children, but some of these were not randomized controlled trials (RCT). The effectiveness in prevention varied from 20-80%. Type 1 and type 2 lepra reactions were 13.2% less frequent in those who had received a BCG vaccine.^{29,30} Vaccination was found to be more effective in females and those less than 20 years of age, as well as in individuals with a BCG scar less than or equal to

5 mm in diameter.³¹ Some of the current research supports the use of BCG vaccine in endemic areas for the prevention of leprosy in children and more research is required to develop this method of leprosy control in the future.

In addition to the development of better vaccines to reduce the spread of Hansen's disease, chemoprophylaxis in contacts of patients with leprosy has also been employed as a method of control. A review of 320 references was carried out and revealed seven RCT, with a total of 66,311 participants, using either single dose rifampicin, dapsone twice weekly for 2 years, or acedapsone every 10 weeks for 7 months, with follow up ranging from 2-4 years.³² In all studies chemoprophylaxis was superior to placebo. A single dose of rifampicin administered to contacts of newly diagnosed leprosy patients was 57% effective in preventing the development of HD after 2 years of follow up. Acedapsone administration reduced the rate of leprosy in contacts by 67%, and Dapsone reduced the rate by 30-40%. The studies did not report adverse events and a significant number of participants were lost to follow up. Rifampin, Ofloxacin, and Minocycline (ROM) has been used as chemical prophylaxis, reducing the serological response development of antibodies to *M. leprae*, but the data was found to only be statistically significant in adults.³³

Treatment of Reactions: Type 1 Reactions

Acute inflammatory reactions may occur in treated and untreated Hansen's disease, and may present as medical emergencies since injury to the nerves develops rapidly, resulting loss of sensation, paralysis (Figure 32-8), and deformities (see Figure 32-3a), and ocular involvement ultimately results in severe visual impairment.³⁴ Chemotherapy for leprosy is not discontinued in the setting of reactions because of its added anti inflammatory effect (Table 32-5).

Type 1 reactions, also known as reversal reactions, occurs in 15-30% of BL, BB and BT leprosy, and are believed to be a result of increased antigen excess resulting in an upgrading of delayed type hypersensitivity.³⁵ Patients present with erythema and edema of existing skin lesions, acral edema, and painful neuritis, which may become severe and last weeks to months.³⁴ Reversal reactions have also been observed following immunization, with other mycobacterial infections, pregnancy, and both physical and emotional stress.³⁵

Corticosteroids have been the first-line treatment and are effective in reducing inflammation and edema of nerves. Prompt treatment with prednisone 1 mg/kg/day is required to prevent irreversible nerve damage.³⁶ The dose of prednisone is increased if there is no response within 24-48 hours and tapered slowly to prevent relapse. High dose steroids are often required for a prolonged period of time and carry a significant risk for serious side effects. The earlier that treatment with corticosteroids is instituted after onset of nerve damage, the greater the likelihood of preventing permanent nerve impairment. Irreversible nerve damage



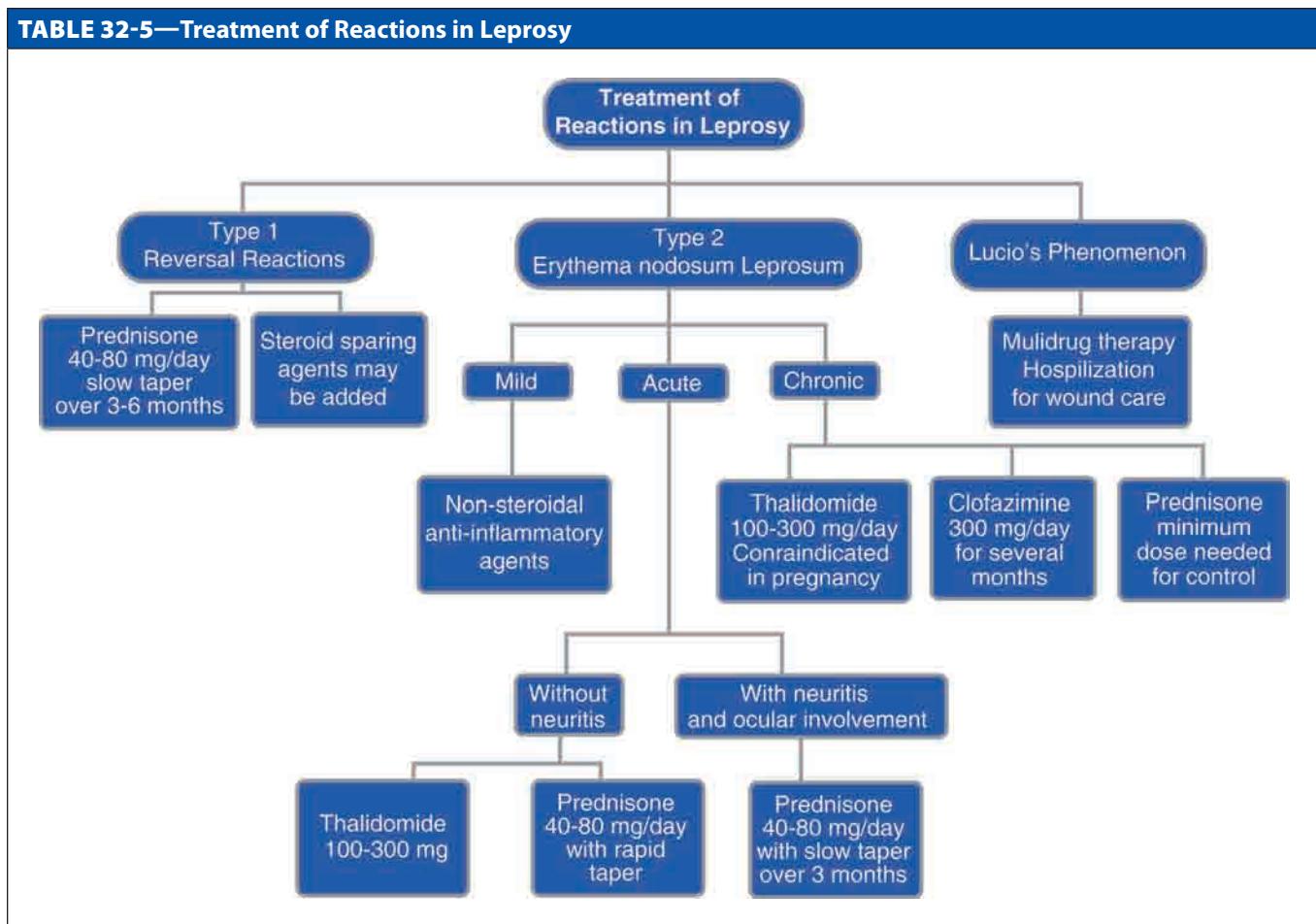
FIGURE 32-8 Borderline lepromatous leprosy patient with acute neuritis of the radial nerve and new rare onset right wrist drop.

can ensue within hours to days and steroids only have a 60% success rate in salvaging nerve function when started early and given over an extended period of time.³⁷

A number of steroid sparing agents have been investigated but the clinical trials are small and more studies are needed to further investigate the role of steroid sparing agents in the treatment of leprosy reactions. Pro-inflammatory cytokine gene expression, such as Interferon (IFN)-gamma, Tumor necrosis factor (TNF)-alpha, Interleukin (IL)-1, IL-2, IL-12, are increased during type 1 reactions.³⁸ Although Thalidomide inhibits TNF-alpha, it was found to have no benefit in treating reversal reactions.³⁹ Cyclosporine, which blocks the transcription of IL-2 and suppresses cellular immunity, has been used successfully to treat reversal reactions but is not as effective as corticosteroids and larger clinical trials are needed to further evaluate its potential use.^{40,41} Pentoxifylline and azathioprim have shown conflicting results. There is one case report using methotrexate to successfully treat a reversal reaction, and there have been no studies investigating the use of mycophenolate mofetil in the treatment of type 1 reactions.⁴²

Several studies have looked at using prednisolone as prophylaxis for neural damage. The results have shown that corticosteroids fail to improve the status of motor and sensory nerves when used as a prophylaxis.⁴³ Furthermore, the studies revealed that nerve conduction studies were abnormal at the onset of treatment, indicating that peripheral nerve damage is more extensive at the time of presentation than had previously been recognized.

Longitudinal epineurotomy, by incising the thickened epineurium and burying the nerve in deeper and warmer tissues, medial epicondylectomy, and decompressive surgery, are frequently used to treat neuritis.⁴⁴ Surgical intervention is always used in combination with medical therapy. Indications for surgery include nerve function impairment, nerve pain, and nerve abscesses; however, the long-term benefits are not well substantiated. There are three randomized controlled trials comparing medial epicondylectomy and corticosteroids with corticosteroids

TABLE 32-5—Treatment of Reactions in Leprosy

Treatment of reactions in leprosy. Type 1 reversal reactions require high dose steroids with a slow taper to preserve nerve function and reduce the risk for relapse. Steroid sparing agents may also be beneficial, but more research is needed to identify effective agents.^{35,36} Type 2 reactions are treated according to their severity and duration with anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs, Clofazimine, Thalidomide, and steroids in severe cases.⁴⁸ The Lucio's phenomenon requires hospitalization and supportive medical care. These patients very rarely present with ENL.⁵⁶

alone in patients that had ulnar nerve neuritis of less than six months duration.⁴⁴⁻⁴⁶ The outcomes for the surgical group and the medical treatment group did not show any significant difference in outcome after one year of follow up. The studies did not report on surgical complications and adverse outcomes, making the data insufficient to draw sound conclusions regarding surgery for treating nerve damage in Hansen's disease. The claw hand deformity on the other hand (Figure 3a), which develops from damage to the ulnar nerve, can be successfully corrected thru surgical intervention with tendon transfers, resulting in a more functional hand and reducing one of the most common stigmas associated with HD.⁵

Treatment of Reactions: Type 2 Reactions

Erythema nodosum leprosum, or type 2 leprae reaction, affects 9% of borderline lepromatous leprosy and 49.4% of lepromatous leprosy patients (Figure 32-9). ENL affects men more frequently than women.⁴⁷ The prevalence of ENL has decreased significantly since the introduction of MDT for MB. The patients present with fever, malaise, painful red nodules affecting the skin, iritis,

myalgias, periosteal inflammation and dactylitis, arthralgias, lymphadenopathy, mastitis, and orchitis.^{6,7} Patients may also develop acute neuritis as a result of antibody-antigen immune complex deposition, dysregulation of macrophages and T-cells, and overproduction of TNF- α . Histology is characterized by a neutrophilic infiltrate in acute lesions. There are randomized clinical trials evaluating the treatment of ENL, however, they are difficult to compare due to the heterogeneity of treatments and small sample sizes used in the trials.⁴⁸ Clofazimine, which has an anti-inflammatory effect, appears to reduce the frequency and severity of Type 2 reactions. One trial compared thalidomide to acetylsalicylic acid and found that treatment with thalidomide resulted in fewer lesions.⁴⁹ Other trials revealed that clofazimine at higher therapeutic dosage had a long-term benefit with fewer recurrences and greater treatment success when compared to thalidomide and prednisolone respectively.^{50,51} There are no trials comparing thalidomide to prednisone for the treatment of type 2 reactions.

There are a number of non-randomized clinical trials that showed that thalidomide was quite effective in the treatment of ENL, its use, however, is limited due to its



FIGURE 32-9 Borderline lepromatous leprosy undergoing MDT presenting with acute erythema nodosum leprosum, consisting of tender erythematous nodules on the arms, which was associated with constitutional symptoms.

teratogenicity, and a potential increase in thromboembolisms, and neuropathy.⁵² Prednisone is also highly beneficial for type 2 reactions and methotrexate, azathioprim, cyclosporine, pentoxifylline, and etanercept are reported to reduce ENL in a number of case reports.⁵³

LUCIO'S PHENOMENON

Antibodies to cardiolipin and SS-B can be seen in lepromatous leprosy. Patients may develop antiphospholipid antibody syndrome characterized by necrosis of the skin and digits secondary to hypercoagulability. This may be misdiagnosed as Lucio's phenomenon (LP).⁵⁴ The LP is a rare acute necrotizing endotheliitis with thrombosis that has been primarily described in patients of Mexican ancestry.⁵⁵ This serious complication has a high morbidity and high mortality rate. The patients present with painful stellate skin ulcerations that have overlying black eschar and involve the face, trunk, and extremities. They have arthralgias, fever, anemia, and cachexia. These patients all have the so-called primary diffuse lepromatous leprosy, "La lepra bonita", they have madarosis, and they may have high levels of cryoglobulins in addition to high levels of *M. leprae* antigens. A retrospective study of 200 skin biopsy specimens from patients with LP revealed five common features: Endothelial cells are heavily laden with acid-fast bacilli, vascular endothelial cell proliferation resulting in vessel wall thickening and obliteration of the

vascular lumen, vascular ectasia, angiogenesis, and thrombosis of cutaneous vessels.⁵⁶ LP requires intensive inpatient management for wounds and supportive medical care, such as that provided by a burn unit, in addition to MDT. The condition carries a 50% mortality, even with advanced medical care and systemic corticosteroids.

COMORBIDITIES

In the United States, 85% of the leprosy cases detected are in immigrants. In the past the majority of cases were identified in refugees and immigrants from Cambodia, Laos, and Vietnam. In the last 10 years the demographics have changed with most patients coming from Brazil. Patients frequently have infectious and parasitic diseases that include tuberculosis, hepatitis B, strongyloides, schistosomiasis, HIV, and the incidence depends on the region from where they have emigrated.⁵⁷ Appropriate serologic testing for HIV, strongyloides and schistosomiasis, in addition to PPD placement, should be carried out at initial presentation. These comorbidities require treatment prior to initiating therapy with immunosuppressive agents.

FOOT CARE

Treatment of the insensitive foot in leprosy is analogous to treatment of the diabetic foot and remains a challenge in HD. A comprehensive treatment plan includes healing ulcerations and reducing the rate of recurrent ulcerations.⁵⁸ Regular debridement of calluses is necessary to reduce the risk for the development of perforating ulcers. (Figure 32-10) Damage to autonomic and sensory nerve fibers of the skin leads to dry skin, the inability to sweat, and loss of local sensation. Dry skin is prone to cracking, ulceration, and secondary infection. Loss of sensation leads to



FIGURE 32-10 The insensitive foot with calluses and neuropathic ulcers. The patient has already lost a number of toes secondary to infected traumatic ulcerations and osteomyelitis.

misuse, callus formation, injury, and secondary infection with development of osteomyelitis and resultant joint deformation. The Gillis W. Long Hansen's Disease Center has developed methods of fabricating cutout sandals (also known as the Carville sandal), walking splints, and walking casts that are used in conjunction with special footwear and patient education to treat and prevent plantar ulcers successfully.

A meta-analysis of interventions for skin changes caused by nerve damage in leprosy was done, but the various trials are difficult to compare due to diverse interventions and outcome measures in the studies.⁵⁹ Zinc tape showed some benefit over other traditional dressings, although the difference was not statistically significant. Casting of the foot and other methods of fixation of the foot aids in the healing of ulcerations. Polyvinyl chloride boots were slightly less effective as canvas shoes, and there was no significant difference in below the knee plasters and double rocker bottom shoes in promoting wound healing. None of the studies commented on complications and RCT are needed to further define best treatment practices for ulcer management and prevention in leprosy.

Additional measures to reduce ulcerations and improve the healing of existing ulcerations include avoidance of long distance walking, reduction of manual workload, and patient education of self-foot care. Patient and family education programs in self-care are effective in reducing ulcer rates by 41% at the end of one year and consistent use of orthotic shoes reduce the ulcer rates by 43%.⁶⁰

Infections and osteomyelitis are common complications of foot ulcerations. The most common bacteria isolated from local wound infections were *Staphylococcus aureus* and *Pseudomonas aeruginosa*.^{58,60} Soft tissue infections require administration of antibiotics and osteomyelitis requires long term antibiotic therapy. Frequently surgical debridement of the infected bone and amputation is necessary to control the infection.

Surgical management of deformities is helpful in reducing the stigma of HD familiar to people living in endemic areas and improving the quality of life of patients. Damage to the peroneal nerve may result in foot drop and the ankle may be stabilized with orthoses or surgical intervention with arthrodesis to allow for better ambulation.⁵⁸

MENTAL HEALTH

Mental illnesses are seen more frequently among patients treated for or with a history of leprosy. The rate of depression is three times higher among Hansen's patients than in patients suffering from other skin conditions such as *Tinea versicolor*.⁶¹ A study from an outpatient leprosy clinic in Ethiopia revealed an even greater increased risk with 52.4% of Hansen's patients reporting as having mental distress when compared to 34.6% of patients suffering from other skin conditions, yet the symptoms were not further classified into specific psychiatric diagnoses. The sex distribution

in this study was equal.⁶² Overall, the data available regarding mental illness in HD is sparse, yet the studies that are published indicate a need to investigate the psychosocial needs of this patient population further in order to integrate the appropriate psychiatric management into our current medical management.

OCULAR COMPLICATIONS IN LEPROSY

There is an increased prevalence in eye diseases among patients with MB disease, some of which may lead to blindness. *M. leprae* prefers the cooler parts of the body, which includes the anterior chamber of the eye. The inflammatory response to the bacillus, scleritis and iritis, may result in posterior synechia and cataracts.⁶³ The iritis is managed with steroid eye drops or oral prednisone. ENL may also affect and damage the eye.

Neuritis of the fifth and seventh cranial nerves can result in insensitivity of the cornea and paralytic lagophthalmus.^{3,5} Data from patients in India with treated MB disease revealed that ocular disease was more frequent when compared to the general population. The prevalence of bilateral blindness was 1.04% (95% confidence interval (CI)), unilateral blindness was 8.55% (95% CI), glaucoma with a mean intraocular pressure of 12 mm HG was 3.6% (95% CI), and cataracts occurred three times more frequently.⁶³

Damage to the ophthalmic division of the fifth cranial nerve results in anesthesia of the cornea and loosing the blink reflex, preventing the patient from noticing if the eyes are dry or if there is something in the eye.^{3,5} Eye drops and antibiotic ointments are helpful in protecting the cornea. If the zygomatic branch of the seventh cranial nerve that innervates the orbicularis muscle is damaged, paralysis and lagophthalmus can ensue, leaving the cornea exposed during sleep and leading to an exposure keratitis and corneal ulceration that will ultimately lead to blindness. Medial and lateral tarsorrhaphy can surgically correct the deformity so that the eyelid can close and protect the cornea.

DETECTION AND TREATMENT OF NEUROPATHY

Early detection and treatment of neuropathy in HD is important in decreasing the degree of permanent sensory and motor impairment. Peripheral nerves and superficial cutaneous nerves are most commonly involved.³ The peripheral nerves become enlarged and tender, and are palpable on examination. These nerves include the greater auricular nerve (Figure 32-11), supraclavicular nerves as they cross the clavicle, the ulnar nerve proximal to the elbow, the dorsal cutaneous branches of the ulnar nerve at the wrist, the median nerve, superficial radial nerves, common peroneal (lateral popliteal) nerves as they course around the neck of the fibula, the superficial peroneal nerves of the anterior ankle, posterior tibial nerve below



FIGURE 32-11 Borderline tuberculoid leprosy patient with an enlarged palpable nerve of the neck.

the medial malleolus, and the sural nerve. The ulnar nerve is the most commonly enlarged and tender nerve.

Monofilament testing (MFT) (Figure 32-12) is the most commonly employed technique to detect and grade the severity of sensory neuropathy. Studies looking at the sensitivity and specificity of the various clinical tools available to assess peripheral nerve function have shown that the sensitivity of MFT was between 35-44% and voluntary muscle testing (VMT) was quite low at 4-5%, although testing of the ulnar nerve was higher at 25%.⁶⁴ By combining nerve palpation with MFT, the sensitivity was increased to greater than 60 % and the combination of the two tests are the most practical methods employed when assessing and treating patients in the field. The sensitivity varied with the nerves palpated: all nerves ranged from 71-88%, with the exception of the sural nerve (59%) and the median nerve (43%). The specificity of nerve palpation was greater than 60% for all nerves, except for the common peroneal nerve (40%) and the ulnar nerve (34%). Thus nerve palpation

is more sensitive but less specific than VMT and MFT in assessing peripheral nerve function in Leprosy since palpable nerves may be present in unrelated medical conditions.

Subclinical neuropathy is quite common in patients and ranges from 20-50%.⁶⁵ Sensory perception was most frequently affected, followed by warmth detection thresholds (WDT) and cold perception thresholds (CPT). In random testing of HD patients, nerve conduction studies of the ulnar nerve revealed that 29% of patients had decreased WDT and 13% had decreased CPT.

The International Federation of Anti-Leprosy Associations (ILEP) Nerve Function Impairment & Reaction (INFIR) Cohort Study in India performed a small study looking at the inter-tester reliability of MFT and VMT.⁶⁶ Good to very good reliability was noted with MFT and moderate reliability was noted with VMT, with individual testers varying up to one grade from the gold standard value. With additional review and correction of discrepancies of the techniques used by the physiotherapists, good reliability was achieved, highlighting the importance of formal training and review of the techniques employed to obtain reliable and consistent results.

Despite successful completion of treatment and no evidence of lepromatous reactions, some patients have a silent neuropathy with asymptomatic progression of sensory and motor loss. The mechanism of this progression is poorly understood and there are no RCT investigating treatments for this type of neuropathy.

NEUROPATHIC PAIN

It is the general belief of both lay people and health care providers that leprosy patients feel no pain. Neuropathic pain is more common than previously recognized and is a rising problem in leprosy. As part of a relapse study carried out in Ethiopia in patients 10 years after completing MDT, 29% reported symptoms consistent with neuropathic pain



FIGURE 32-12 (A) Sensory testing can be carried out using nylon filaments of different diameter, allowing to grade the degree of loss of sensation. (B) Monofilament testing of the acral surface of the left foot.

that was described as being severe.⁶⁷ The neuropathic pain is generally refractory to analgesics such as non-steroidal anti-inflammatory drugs and opioids.

Proposed mechanisms of the development of neuropathic pain include spinal sensitization, sprouting of A beta nerve fibers in the superficial layer of the dorsal horn, and ectopic discharge in the dorsal root ganglion or in a neuroma of a nerve stump.⁶⁸ The ectopic discharge is mediated by sodium channels can be blocked by anticonvulsants and lidocaine. The emphasis has been on leprosy control programs and worldwide distribution of multi drug therapy and little attention has been given to the treatment of pain associated with HD. Treatment is limited to gabapentin, amitriptyline, and serotonin reuptake inhibitors and no RCT evaluating their efficacy have been carried out. Research is needed to address this treatment challenge.

NEW BACTERIA CAUSING LEPROSY

In 2009, a new bacterium, called *Mycobacterium lepromatosis*, causing leprosy was described and characterized.⁶⁹ It shares 90.9% homology with *M. leprae* and represents a divergent species. The new bacterium was isolated from two patients in Mexico with diffuse lepromatous leprosy who died from their disease. It has been proposed that this new species is associated with LL and perhaps LP, which may explain regional differences in HD and the increased incidence of LP in Mexico. At this time the treatment for *M. lepromatosis* is the same as employed for *M. leprae*.

CONCLUSION

The two important events in the history of treatment of leprosy was; the Miracle at Carville with the discovery of promin's ability to cure HD, and the development of MDT by the WHO in greatly reducing the number of active cases of leprosy to just over 200,000 annually world-wide since the 1980's. More than 15 million people with leprosy have been cured using MDT. Although the WHO does not count those individuals who have completed MDT, these patients continue to suffer significant morbidity secondary

to ocular and nerve involvement, due to ongoing reactions, which in the case of LL can last up to 10 years after treatment until the immune system has been able to clear all bacterial remnants from tissues. The insensitive feet and hands are continuously subject to trauma and infections, resulting in deformities. Consequently, these patients require life-long ongoing medical care.

The number of annual new cases of leprosy has not decreased significantly over the last 10 years and new efforts directed to control transmission thru vaccines and chemoprophylaxis have been explored, but due to the long incubation period before disease becomes evident (average 2-7 years), and the challenge in collecting appropriate data, large multicenter long-term trials have been difficult to conduct.

Lepromatous reactions and their treatment are complex and their immunological mechanisms are still poorly understood. RCT are needed to identify additional treatment options available and to explore steroid sparing agents that can control reactions and preserve nerve function. There has been a lack of funding for trials of this nature as most of the efforts by the WHO have been dedicated to the WHO Leprosy elimination program to reduce the prevalence of leprosy cases to less than 1 per 10,000 people with their MDT program. Hansen's disease is a good research model for granulomatous diseases. Clinical trials are also needed to evaluate the psychological needs of patients with HD and how to better treat neuropathic pain; both problems have been under recognized.

The results of existing trials in the field of leprosy are difficult to interpret and compare due to the heterogeneous treatments used, small sample size of patients, and often a lack of reporting of adverse events and outcomes. Future trends in treatment and management of leprosy includes the treatment of contacts and vaccines to reduce transmission. The relapse rate of leprosy remains low, but existing cases may be secondary to the under diagnosis of MB by merely counting skin lesions, and treating all HD patients with MDT for two years would eliminate this problem. The rate of resistance of bacilli to MDT also remains low and the treatment of choice for leprosy is MDT as recommended by the NHDP and the WHO.

What We Know

- There are two bacteria that cause leprosy: *Mycobacterium leprae* and *Mycobacterium lepromatosis*.
- MDT as recommended by the NHDP and the WHO is an effective treatment to cure leprosy. The relapse and resistance rates remain low with this treatment.
- Early recognition and treatment of HD is the most important factor in reducing the degree of neuropathy and disability that the patient may ultimately develop.
- BCG vaccines are effective in reducing the infection rates with leprosy in children by 20-80%. Vaccination also reduces the rate of lepromatous reactions in patients with HD by 13.2%. The benefit of BCG vaccination is greatest in children and women.
- Chemoprophylaxis in contacts of patients with leprosy is effective in decreasing the rate of development of HD in these contacts by 30-67%. Treatment was most effective with Acedapsone, followed by Rifampicin, Dapsone, Minocycline and ROM.

(Continued)

What We Know (Continued)

- The insensitive foot requires wearing orthotic shoes daily, which will reduce the risk for the development of plantar ulcers by 43%. Patient self-care education programs are effective in healing of existing ulcers and in decreasing ulcer formation of the feet by 41%.
- Type 1 reactions occur in 15-30% of borderline leprosy patients and prednisone 1 mg/kg/day is effective in controlling neuritis, but must be tapered slowly to prevent relapse. Prompt recognition and treatment is essential to reduce the neuropathy and deformities associated with damage to the involved nerves. Even with aggressive treatment, the neuropathy progresses in 60% of patients.
- Type 2 reactions occur in 9% of borderline leprosy patients and in 49.4% of LL patients. Clofazimine and Thalidomide are helpful in controlling ENL, as is prednisone. The medications are titrated to the lowest dose required to control the reaction.
- Pregnancy is associated with an increased frequency of reactions: 50% will develop Type 1 reactions during the postpartum and lactation period, and 68% will develop Type 2 reactions during the third trimester and the postpartum and lactation period.
- The Lucio's phenomenon is a vasculopathy associated with diffuse LL and is most common in patients of Mexican ancestry. The disease carries a 50% mortality rate and requires intensive supportive medical care and wound management.
- Ocular disease is common in HD and requires specialty care to manage and reduce morbidity and the risk for blindness.
- Both mental illness and neuropathic pain are seen with increased frequency in HD and RCT are needed to address the treatment of these conditions.
- Surgical correction of deformities are beneficial in improving functionality of the hands and feet, the quality of life of those with HD, and also are important in reducing the stigma associated with this disease and its socio-economic impact.

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Treatment of Cutaneous Lupus Erythematosus

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INTRODUCTION

Systemic lupus erythematosus (SLE) is a systemic autoimmune disease capable of damaging all organ systems, resulting in a myriad of clinical presentations. The diagnosis of SLE, for research purposes, is defined by the 1982 American College of Rheumatology criteria.¹ Cutaneous manifestations of disease are seen in up to 90% of patients with SLE.² These cutaneous findings have been categorized into lupus-specific and lupus nonspecific lesions, based on their histologic appearance.³ Lupus-specific lesions are also broadly referred to as cutaneous lupus erythematosus (CLE). CLE has been further subcategorized based on the clinical morphology of the lesions and their average duration.³ The subcategories of CLE are chronic cutaneous lupus erythematosus (CCLE), subacute cutaneous lupus erythematosus (SCLE), and acute cutaneous lupus erythematosus (ACLE).³ Chronic cutaneous lupus erythematosus (CCLE) is further divided into the following subsets: classic discoid lupus erythematosus (DLE), generalized DLE, hypertrophic DLE, lupus profundus, lupus erythematosus tumidus, and chilblain lupus. Limited DLE is the most common form of CLE. When confined to the head and neck, it is rarely associated with SLE. DLE resolves with scarring and dyspigmentation. SCLE presents with photodistributed erythematous polycyclic patches or psoriasiform lesions. SCLE is transient and heals without scarring. SCLE is commonly associated with anti-SS-A antibodies and photosensitivity. Approximately 50% of patients with SCLE will meet ACR criteria for SLE.⁴ Acute cutaneous lupus erythematosus (ACLE) most often presents as an erythematous malar rash, although a generalized variant can occur. Close to 100% of patients with ACLE have SLE, making it the most specific cutaneous marker of systemic disease.^{4,5} It is also important to note that not all patients with CLE have SLE. CLE is two to three times more prevalent than SLE.⁴ Quality of life measures reveal that CLE is associated with significant morbidity.⁶

EPIDEMIOLOGY

A recent study by Durosaro et al.⁷ in a predominantly Caucasian population estimated the incidence of CLE as 4.3 per 100,000. A study of SLE in a similar population revealed an incidence of 3.06 per 100,000.⁸ Prior authors

have estimated that CLE is two to three times more prevalent than SLE.⁴ Both CLE and SLE are most prevalent in blacks, and in women of childbearing age.

ETIOLOGY

The etiology of CLE remains unknown. It is hypothesized that a unique combination of genetic predisposition, ultraviolet light (UVL) exposure, and immunologic factors results in the cutaneous, and possibly systemic, manifestations of the disease.^{9,10} Recently, several reviews of the pathophysiology of cutaneous lupus have been published^{9–11} A brief summary of these reviews follows. Multiple genes have been associated with the formation of CLE. Particularly, polymorphisms in genes encoding HLA subtype, tumor necrosis factor α , and complement molecules have been described. UVL exposure has an important role in pathogenesis. UVL is known to cause suprabasilar keratinocyte apoptosis. During apoptosis, these suprabasilar keratinocytes form outer membrane blebs full of self-antigens. Noninflammatory clearance of these apoptotic cells is impaired in patients with CLE, likely secondary to complement abnormalities, particularly a decrease in C1q. These apoptotic keratinocytes are thus phagocytosed, and the blebs that contain self-antigen are then presented to the host immune system, resulting in the formation of autoantibodies. The cellular debris of the UVL-induced apoptotic cells is also able to induce plasmacytoid dendritic cells, through Toll-like receptors 7 and 9, to make IFN- α . IFN- α induces cytokines involved in lymphocyte recruitment (CXCL9, CXCL10, CXCL11). These lymphocytes, once recruited to the skin, participate in cell-mediated destruction of the basement membrane. Lymphocytes are further recruited by the UVL induced production of cytokines IL-1 and TNF- α , and adhesion molecules ICAM-1, VCAM-1, E-selectin. This cascade, induced by UVL and propagated by the immune dysregulation in the patient, explains the combination of humoral and cell-mediated autoimmunity seen in CLE.

OUTCOMES MEASURES

Prior studies evaluating therapeutic options for CLE are difficult to interpret given the relative rarity of the disease, and the lack of a uniform outcome measure. Prior

investigators have used SLE activity indices such as the Systemic Lupus Activity Measure (SLAM) or the Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) to monitor patient improvement (for review of activity indices see.¹²) However, neither of these indices are sensitive or specific for cutaneous improvement. Case reports and case series generally report subjective improvement by the investigator. This inability to measure outcomes made multicenter trials and systematic reviews impossible to conduct. In 2005, the Cutaneous Lupus Erythematosus Disease Area and Severity Index (CLASI) was introduced as an outcome instrument for CLE¹³. The CLASI reports two separate numerical scores: one for disease activity, and one for damage. The CLASI is a validated measure for both Dermatologists and Rheumatologists¹⁴ and will hopefully transform our ability to conduct meaningful objective studies of CLE.

SEARCH METHODOLOGY

We searched the Cochrane Library (Issue 3, 2009), Medline and Embase from inception until September of 2009, as well as the reference lists of relevant reviews.

RESEARCH QUESTIONS

Are Antimalarials Effective in the Treatment of Cutaneous Lupus?

During World War II, it was observed that soldiers with rheumatoid arthritis and systemic lupus erythematosus had less disease activity while on antimalarials.¹⁵ Since that time, antimalarials have been used for both SLE and CLE. Antimalarial efficacy is postulated to be associated with their photoprotective abilities, lysosomal stabilization, antigen presentation suppression, effects on toll receptors, and inhibition of prostaglandin and cytokine synthesis.^{15,16} Antimalarials also decrease TNF- α expression.¹⁷

Landmark studies for the use of antimalarials in SLE include the Canadian withdrawal trial published in 1998,¹⁸ and a recent systematic review of the effects of antimalarials on SLE outcomes.¹⁹ Ruiz-Irastorza et al. found that patients with SLE treated with antimalarials had significantly fewer lupus flares, increased survival, decreased thrombosis, and increased protection against irreversible organ damage (Ruiz-Irastorza, Ramos-Casals et al. 2009). Studies assessing use of antimalarials in CLE are limited.

We found two double-blind randomized controlled trials involving antimalarials.

The first, published by Ruzicka et al. in 1992 assessed the efficacy of acitretin compared to hydroxychloroquine in the treatment of CLE. 58 patients were randomized to either receive acitretin (28 patients) or hydroxychloroquine (30 patients). The patients were treated for 8 weeks. The outcome was defined as subjective improvement by a blinded investigator. Four patients in the acitretin

arm dropped out because of side effects. Three patients in the hydroxychloroquine group dropped out because of complete clearing of their cutaneous lesions. Thirteen out of 28 (46.4%) of patients treated with acitretin improved compared to 15 out of 30 (50%) patients treated with hydroxychloroquine. The difference in the results is not statistically significant. Patients reported increased side effects with acitretin compared to hydroxychloroquine. This study is limited by its short treatment period. Hydroxychloroquine is not at peak levels until 12 weeks of therapy.²⁰

The second, published by Bezerra et al. in 2005, assessed the efficacy of clofazimine in comparison to chloroquine. Thirty-three patients with CLE who met criteria for SLE were enrolled. Sixteen patients were randomized to receive clofazimine and 17 patients were randomized to receive chloroquine. The patients were followed for 6 months. Patient improvement was measured via the Mexican version of the SLEDAI (MEX-SLEDAI). The MEX-SLEDAI is a modified version of SLEDAI that does not include immunotesting. Scores are reported as 0 to 101, with only two possible points for rash assessment. Improvement was defined as an increase in the SLEDAI score by 5 overall. The study was conducted with intention to treat analysis. Five patients in the clofazimine group, and one patient in the chloroquine group dropped out of the study secondary to flares of their SLE. Twelve out of 16 (75%) of patients in the clofazimine group improved. Fourteen out of 17 (82.4%) patients in the chloroquine group improved. There was not a statistically significant difference in outcome between the clofazimine group and the chloroquine group. Clofazimine causes significant skin discoloration, which limits its use. One patient in the clofazimine group had a significant systemic flare.²¹

Kraak et al. published a double blind nonrandomized trial comparing hydroxychloroquine to placebo in patients with DLE. A total of 49 patients were treated for 1 year. Twenty-four patients received hydroxychloroquine, and 25 patients received placebo. At the end of 1 year, based on a subjective examination performed by an investigator, patients on hydroxychloroquine were improved over placebo.²²

Multiple case series have also been published supporting the use of antimalarials in CLE. In 1957, Christiansen published a review of multiple case series, totaling 414 patients with CLE treated with chloroquine. He reported that 265 of the patients (64%) had an improvement on the high dose (500 to 750 mg) of chloroquine used at that time (Christiansen 1957).

A case series published by Callen in 1982 reported 30/34 (88%) of patients with DLE improved on hydroxychloroquine (Callen 1982).

Kreuter et al. published a retrospective review of 36 patients with tumid lupus treated with antimalarials. They reviewed the charts of twenty-six patients treated with chloroquine and ten treated with hydroxychloroquine.

Improvement was scored with a retrospective CLASI. The authors do not describe how they determined the retrospective CLASI score. They report 61% of patients exhibited complete or almost complete clearance of lesions with CLASI scores of 0 to 1. They found no difference in the efficacy of chloroquine compared to hydroxychloroquine. Only those patients on chloroquine reported side effects of headache, dizziness and nausea.²³

We found two studies looking at the addition of quinacrine in refractory patients. Toubi et al. retrospectively evaluated the addition of quinacrine to plaquenil in six patients with refractory SLE. Three of the six patients had skin involvement at the beginning of study. All six patients had been on plaquenil for approximately 2 years, as well as low dose steroids and methotrexate or azathioprine. All six patients had SLEDAI scores over 5. Quinacrine, 100 mg per day, was added to the current therapy. Five out of six patients had improvement in their SLEDAI scores. All three patients with CLE had improvement in their SLEDAI scores, but the authors do not report if this was secondary to improvement in their cutaneous findings. Two out of the three patients with CLE stopped the quinacrine during the study for a pregnancy. Both flared with quinacrine cessation, and both had improvement in their SLEDAI scores with reinstitution of the medication after delivery.²⁴

Cavazzana et al. conducted a retrospective cohort analysis of 34 patients looking at the addition of quinacrine in patients with skin disease unresponsive to hydroxychloroquine. Two different doses of quinacrine were used (50 mg/d in 5 patients and 100 mg/day in 29 patients). Responses were graded by a retrospective CLASI score. Complete response was defined as no remaining lesions. Partial response was defined as at least a 50% reduction in CLASI. Twenty-five out of 34 patients (73.5%) had a partial response. The dose of quinacrine did not affect the response, but higher doses of quinacrine did result in a statistically significant more rapid improvement. Side effects were reported in ten of 30 patients (8.8%) and included yellow discoloration and a hepatitis flare in a patient with underlying Hepatitis C. Eighteen out of 34 patients (52.9%) stopped quinacrine (nine because of no response, two because of a clinical remission, three because of side effects, three "voluntarily stopped", and one because of pregnancy). This study is limited by its retrospective nature, the small sample size, and the high drop out rate. Quinacrine induced a partial response in patients' refractory to hydroxychloroquine in approximately 75% of patients, but was not tolerated by some patients.²⁵

TOXICITY

The most commonly reported side effects of antimalarials are nausea, gastrointestinal upset, and headache. Hydroxychloroquine can cause blue-grey discoloration of the skin. Quinacrine causes yellow discoloration of the skin and sclera. The risk of retinal toxicity is minimized with

ideal body weight-based dosing (less than 6.5 mg/kg/day for hydroxychloroquine and less than 3.5 mg/kg/day for chloroquine).²⁶ Chloroquine has a higher risk of retinal toxicity than hydroxychloroquine, particularly if given for prolonged periods.²⁷ Two systematic reviews support the safety of hydroxychloroquine use during pregnancy.^{19,28}

CONCLUSIONS

There are no randomized controlled trials of antimalarials compared to placebo in the treatment of CLE. Randomized controlled trials comparing antimalarial efficacy in comparison to acitretin and clofazimine reveal 50% of patients on hydroxychloroquine improve at 8 weeks, and approximately 82% of patients on chloroquine improve by 6 months. These percentages are supported by a large case series of patients with CLE treated with antimalarials. Systematic reviews reveal obvious benefits of antimalarials in treating SLE. Chloroquine may be more efficacious than hydroxychloroquine, but chloroquine is less well tolerated. Addition of quinacrine appears to be helpful for refractory patients, but may be rarely limited by side effects. There is little evidence of toxicity from antimalarials.

Are systemic Steroids Effective in the Treatment of Cutaneous Lupus?

We did not find any RCT of oral steroids in the treatment of cutaneous lupus. As part of an observational study of patients with DLE,²⁹ reported that 2/25 patients responded to systemic steroids.²⁹

Toxicity

The adverse effects of systemic corticosteroids are well known. Systemic corticosteroids increase blood pressure and blood glucose levels, and predispose patients to osteoporosis, avascular necrosis of the hip, weight gain, depression, and glaucoma.

CONCLUSIONS

There is insufficient evidence to recommend systemic corticosteroids in the treatment of CLE.

Are systemic Retinoids Effective in the Treatment of Cutaneous Lupus?

We did not find any randomized controlled trials assessing the efficacy of systemic retinoids in CLE compared to placebo. One randomized controlled trial assessing the efficacy of acitretin compared to hydroxychloroquine was covered in the antimalarial section above.²⁰ This study is limited by its lack of placebo arm, as well as its short duration of 8 weeks. Hydroxychloroquine has not reached full

efficacy by 8 weeks. Acitretin was found to be as effective as hydroxychloroquine at 8 weeks, but was less well tolerated.

Prior to the publication of their 1992 randomized controlled trial, Ruzicka et al. conducted an open pilot study of acitretin in the treatment of CLE. Twenty patients with CLE were treated with acitretin (10 mg to 50 mg per day) for 4 to 12 weeks. Fifteen of the 20 patients (75%) showed an excellent or good response, defined as complete clearing or moderate clearing of residual lesions.³⁰

Ruzicka et al. also published a case series of 19 patients with CLE treated with etretinate. They reported 11 of 16 patients (69%) improved over a course of 2 to 6 weeks.³¹

Shornick et al. published a case series of 6 patients with CLE refractory to systemic corticosteroids and antimalarial therapy treated with 1 mg/kg/day isotretinoin. They reported clinical improvement in all 6 cases, and disease recurrence with medication withdrawal.³²

Multiple additional case reports of clinical improvement of CLE treated with systemic retinoids have been published. Case reports are limited by selection bias, because negative results are frequently not reported^{33–38}.

Toxicity

Retinoids are well known teratogens. The cutaneous side effects of retinoids are well known and consist of drying of the mucous membranes and skin, hair loss, and pruritus. Retinoids require monthly lab monitoring for pregnancy, decrease in blood counts, and elevations in triglycerides and transaminases.

CONCLUSIONS

There is insufficient evidence to recommend the use of systemic retinoids in the treatment of CLE.

Is Thalidomide Effective in the Treatment of Cutaneous Lupus?

We did not find any randomized controlled trials to support the use of thalidomide.

There are a multitude of case series (defined as greater than five patients) that support the efficacy of thalidomide. Gorrhans and Illy reviewed and summarized all published case series of CLE treated with thalidomide prior to 1984. They described benefit in approximately 90% of 156 patients treated with 100 to 200 mg of thalidomide per day.³⁹

Since this initial case series, 14 additional case series of patients with CLE refractory to other accepted treatment modalities (antimalarials, topical and systemic steroids, methotrexate) have been published. These 14 case series total 361 patients, 308 of whom responded to thalidomide therapy (85%). The treatment length varied from months to years. Many of the case series include a subset of patients

who were weaned off the thalidomide once clinical remission was obtained, and subsequently had disease flares. The patients who flared when weaned off thalidomide universally improved once the medication was reinstated.^{40–53}

Toxicity

The most common side effect reported, in up to 77% of patients, was drowsiness and constipation.⁴⁹ Reports of peripheral neuropathy ranged from 0% to 57% of patients. Thalidomide is a teratogen, causing phocomelia if taken during gestation. Rarely, women of childbearing age have been reported to experience premature ovarian failure while on thalidomide. For this reason, women who are considering having a family should refrain from taking thalidomide.^{54,55}

CONCLUSION

No randomized controlled trials exist to support the use of thalidomide in CLE. Thalidomide has been reported to be successful in the treatment of more than 400 patients with CLE refractory to accepted first line therapies. Randomized-controlled trials are needed to better elucidate the benefits of thalidomide in CLE, particularly given the well-documented severe risks of this medication.

Is Methotrexate Effective in the Treatment of Cutaneous Lupus?

We did not find any randomized-controlled trials of methotrexate in the treatment of CLE.

A double-blind randomized-controlled trial of methotrexate in the treatment of SLE was conducted by Carneiro et al. Forty-one patients with SLE were enrolled. Twenty patients were randomized to receive methotrexate (15 to 20 mg/week) and 21 patients were randomized to the placebo arm. Outcomes were defined as a decrease in SLEDAI scores, a decrease in scores for the visual analog for articular pain, and a decrease in prednisone dose. Baseline numbers for patients with CLE were not recorded. At the end of the study, 16 of the 21 patients (76%) in the placebo arm had cutaneous lesions, whereas only 3 of the 20 patients (15%) in the methotrexate arm had cutaneous lesions. Patients in the methotrexate arm had significantly decreased pain scores, SLEDAI scores, and prednisone doses.⁵⁶

Two retrospective studies of methotrexate treatment of CLE have been published.

Boehm et al. retrospectively reviewed methotrexate use in 12 patients with CLE who failed oral steroids and antimalarials. All patients received 10 to 25 mg of methotrexate (orally or intravenously) weekly. Ten of twelve patients were reported to have improved (six with complete clearing, and four with partial clearing). One patient each was

treated with concomitant oral and topical steroids. The methotrexate was well tolerated, with mention of only mild increases in transaminases. The number of patients who experienced this side effect was not reported.⁵⁷

Wenzel et al. retrospectively reviewed 43 patients with CLE treated with methotrexate. The investigators used a clinical activity index (CLAI) with parameters of extent of skin involvement, inflammation, and clinical course, to assign patients a baseline score, and a score after 2 to 3 months of treatment. Methotrexate was given at a dose of 15 to 25 mg intravenously weekly. Based on CLAI scores, 42 out of 43 patients (98%) improved on weekly intravenous methotrexate. Seven of the 43 patients (16%) stopped the methotrexate secondary to side effects or lab abnormalities (four for elevated transaminases, one because of fatigue, one for pancytopenia, and two patients did not have described reasons for cessation). Gastrointestinal symptoms and fatigue were commonly reported side effects. Moderate elevation in liver enzymes occurred in 23 of 43 patients (54%).⁵⁸

Multiple case reports of improvement of CLE treated with methotrexate exist in the literature.⁵⁹⁻⁶³

Toxicity

Methotrexate is incompatible with pregnancy. It is generally well tolerated with changes in transaminases, headache, fatigue, and gastrointestinal upset; the most commonly reported side effects.

CONCLUSIONS

There are no randomized-controlled trials assessing the use of methotrexate in the treatment of CLE. There is insufficient evidence to guide the use of methotrexate in CLE at this time.

Is Mycophenolate Mofetil Effective in the Treatment of Cutaneous Lupus?

We did not find any randomized-controlled trials using mycophenolate as a therapy for CLE.

Kreuter et al. recently published a prospective nonrandomized open pilot study using mycophenolate sodium in the treatment of ten patients with SCLE resistant to at least one standard therapy. Mycophenolate sodium was given at a dose of 1440 mg per day (which is equivalent to 2000 mg of mycophenolate mofetil per day) to all ten patients for a duration of 3 months. CLASI scores and use of 20MHz ultrasound combined with colorimetry were used to assess outcomes. There was a statistically significant decrease in the mean CLASI score, ultrasound assessment revealed a return to normal thickness, and colorimetric measurement showed statistically significant decrease in erythema⁶⁴.

There are six prior case reports showing improvement in all subtypes of CLE in 11 of 19 patients treated with mycophenolate mofetil⁶⁵⁻⁷⁰.

Toxicity

The most commonly reported side effect of mycophenolate mofetil is gastrointestinal upset and diarrhea. Mycophenolate sodium causes fewer gastrointestinal symptoms than mycophenolate mofetil. In the aforementioned pilot study, Kreuter et al. reported one patient with elevated liver transaminases that reverted to normal once the medication was stopped. Mycophenolate is a relatively new medication, and the long-term ramifications of infection and malignancy risk are unknown.

CONCLUSIONS

There is insufficient evidence to support the use of mycophenolate at this time.

Is Dapsone Effective in the Treatment of Cutaneous Lupus?

We found no randomized-controlled trials of dapsone in the treatment of CLE.

We found three case series assessing the use of dapsone in CLE.⁷¹⁻⁷³ These series make up a combined 55 patients, thirty of whom reportedly improved. We found case reports showing improvement in patients with SCLE, Lupus profundus, DLE, and bullous lupus⁷⁴⁻⁷⁸. Dapsone doses ranged from 25 mg per day to 150 mg per day.

Toxicity

Dapsone can cause a rare hypersensitivity reaction, which results in agranulocytosis. Dapsone causes hemolysis, and therefore some degree of anemia, in all patients. Patients with a deficiency in glucose-6-phosphate dehydrogenase (G6PD) are particularly sensitive to dapsone-induced hemolysis. For this reason, patients should be tested for G6PD deficiency prior to starting the medication. Those patients with G6PD deficiency should not be prescribed dapsone. Dapsone is also known to cause a reversible motor neuropathy. Patients should be monitored for this side effect.

CONCLUSIONS

There is insufficient evidence for the use of dapsone in CLE. Dapsone is anecdotally considered first line therapy in bullous lupus, but this is not supported by any clinical trials.

Are other Systemic Agents Effective in the Treatment of Cutaneous Lupus?

Azathioprine

We did not find any randomized-controlled trials assessing the usefulness of azathioprine in the treatment of CLE.

We found three case reports totaling nine patients with CLE treated with azathioprine. Tsokos et al. reported one patient with generalized DLE who improved with azathioprine.⁷⁹ Ashinoff et al. reported two patients with refractory DLE of the palms and soles who improved with azathioprine.⁸⁰ Callen et al. reported a series of six patients with CLE treated with azathioprine. Three of the six cleared; however all three necessitated cessation of the medication secondary to side effects (drug fever, pancreatitis, and nausea).⁸¹

Rituximab

We found four case reports in the literature documenting improvement of CLE after treatment with rituximab.⁸²⁻⁸⁵

IVIG

We found five case reports in the literature documenting improvement of CLE after treatment with IVIG.⁸⁶⁻⁹⁰

CONCLUSIONS

There is insufficient evidence to support the use of azathioprine, rituximab, or IVIG in the treatment of CLE.

Are Topical Steroids Effective in the Treatment of Cutaneous Lupus?

We found one randomized controlled trial comparing a high potency steroid with a low potency steroid in the treatment of CLE.

Roenigk et al. conducted a 12-week randomized-controlled crossover study comparing 0.05% fluocinonide cream to 1% hydrocortisone cream in the treatment of CLE. Seventy-eight patients were enrolled. Fifty-nine completed the entire 12-week study. A single lesion was chosen for treatment in each patient. A numeric scale from 1 to 5 was used to assess improvement (1 represented worsening and 5 represented clearing). At 6 weeks excellent response was seen in ten of the 37 patients (27%) in fluocinonide arm and four out of 41 patients (10%) in hydrocortisone arm.⁹¹

Ullman et al. conducted a double blind randomized placebo controlled study of R-salbutamol in the treatment of DLE. They enrolled 37 patients with at least one new active lesion of DLE. The primary outcome was change in an invalidated modification of the CLASI, and intention to treat analysis was not carried out. After eight weeks of treatment, the change in the modified CLASI scores in

treated and untreated groups was equivalent. The change in the following secondary outcome measures did reach statistical significance: scaling, hypertrophy, induration, pain, itching, and patient global assessment.⁹²

Barikbin et al. conducted a double-blind prospective comparison of pimecrolimus 1% cream and betamethasone 17-valerate 0.1% cream in the treatment of 10 patients with DLE. The primary aim was comparison of the changes in means of an invalidated skin score. There was no statistically significant difference between the two groups. Using each patient as their own control, each group mean showed a statistically significant improvement.⁹³

Björnberg and Hellgren used a half side of body comparison study to assess the efficacy of fluocinolone acetonide ointment in the treatment of DLE. They enrolled twenty patients. Seventeen of the patients had improvement of the treated half of their body in comparison to the untreated half of their body.⁹⁴

We found two observational studies showing improvement in CLE lesions with topical steroid treatment.^{95,96}

Toxicity

Potent topical steroids are known to cause skin atrophy and telangiectasias, particularly on the thin skin of the face.

CONCLUSIONS

There is good evidence supporting the use of potent topical steroids in the treatment of DLE. Pimecrolimus 0.1% cream is not inferior to betamethasone 17-valerate 0.1% cream.

Are Calcineurin Inhibitors Effective in the Treatment of Cutaneous Lupus?

We found one randomized-controlled trial comparing the use of topical 0.1% tacrolimus ointment with 0.05% clobetasol propionate ointment.

Tzung et al. conducted a randomized-controlled double-blind bilateral comparison study of 0.1% tacrolimus ointment and microdermabrasion versus 0.05% clobetasol propionate ointment and microdermabrasion in 20 patients with CLE (thirteen with ACLE, four with DLE and one with SCLE). The patients were instructed to apply tacrolimus twice daily to one-half of their face, and clobetasol propionate twice daily to the other side of their face for 4 weeks. Improvement was assessed on a seven-point scale each for erythema, desquamation, and induration. The agents were equally effective in obtaining a partial response over a 4-week time course with the addition of microdermabrasion. Clobetasol was noted to cause a statistically significant increase in post-therapy telangiectasias compared to tacrolimus. The results of this study are difficult to interpret given the unconventional addition of microdermabrasion.⁹⁷

Several open label trials were conducted to evaluate the effectiveness of topical calcineurin inhibitors.^{98–103}

Yoshimasu et al. treated nine patients with CLE with 0.1% tacrolimus ointment once daily for 4 weeks and reported improvement in four of their patients.

Kanekura et al. designed a half face comparison study in 3 patients with ACLE. Patients were instructed to apply 0.1% tacrolimus ointment to half of their face twice daily for three weeks. The authors report resolved erythema of the treated side in all three patients.

Lampropoulos et al. treated twelve patients with CLE with 0.1% of tacrolimus ointment twice daily for 6 weeks. Eleven of their twelve patients completed the study. Six patients were reported to have improved based on clinical photographs, clinician opinion, and patient opinion.

Heffernan et al. treated five patients with DLE with 0.1% tacrolimus ointment. Two lesions were chosen in each patient for treatment. Patients were instructed to apply the ointment twice a day for a total of 12 weeks. A clinical scoring system based on diameter, erythema, scarring, and thickness was constructed by the authors. Only three of the five patients completed the study. Using the last observation carried forward they reported that all five patients improved. Based on their scoring system, mean improvement ranged from 32% (reduction in erythema) to 56% (reduction in lesion thickness).

Tlacuilo-Parra et al. conducted an open label trial of twice daily pimecrolimus 1% cream in patients with CLE. Again, a clinical severity score was used to assess clinical improvement in the ten enrolled patients. They report a mean improvement in severity score of 52%.

We found one retrospective cohort study comparing the efficacy of 0.3% tacrolimus ointment combined with 0.05% clobetasol propionate ointment compared to 0.1% tacrolimus alone in the treatment of CLE. Madan et al. reviewed the charts of thirteen patients with CLE who were treated with a combination of 0.3% tacrolimus ointment and 0.05% clobetasol propionate ointment. They report that eleven of the thirteen patients treated with this combination improved (85%). They compared this to five patients who were treated with 0.1% tacrolimus ointment alone. Of the tacrolimus only group, only one patient improved (20%). Two patients in the 0.3% tacrolimus ointment combined with 0.05% clobetasol propionate ointment group developed acne and telangiectasia.

Multiple case reports and case series have also been published showing improvement of CLE when treated with topical calcineurin inhibitors.^{101,102,104,105} A total of eighteen patients have been reported in this manner with 16 reported to have improvement in their cutaneous lesions.

Toxicity

The most commonly reported side effect was a burning sensation. Calcineurin inhibitors have a black box warning for increased risk of lymphoma. There is significant debate

if this is a warranted label for the topical formulations of these medications.

CONCLUSIONS

There is evidence that 0.1% tacrolimus ointment is as efficacious as a potent topical steroid in the treatment of DLE, with less risk of cutaneous side effects.

Is Smoking Cessation Effective in the Treatment of Cutaneous Lupus?

We found no randomized controlled trials assessing the efficacy of smoking cessation in treatment of CLE.

Moghadam-Kia et al. performed a prospective cross-sectional analysis of 114 patients with CLE. Eleven out of the 114 patients had refractory disease, defined as active inflammation in the setting of aggressive systemic therapy. Within this subset of refractory patients, there was a statistically significant increased rate of smoking.¹⁰⁶

We found three retrospective cohort studies.

Rahman et al. performed a retrospective cohort study of 36 patients with CLE whose smoking status was documented in the medical record. All 36 patients were treated with a year-long course of antimalarials. Seventeen smokers and 19 nonsmokers were evaluated after 6 months and 12 months of antimalarial treatment. The primary end point was resolution of CLE. They found a statistically significant difference in the two groups. Three of the 17 smokers (18%) had resolution of their CLE, whereas nine of the nineteen nonsmokers (47%) had resolution of their CLE.¹⁰⁷

Jewell and McCauliffe reviewed the records of 61 patients with CLE who were previously treated with an adequate trial of antimalarials (defined as 8 weeks of hydroxychloroquine or 5 weeks of chloroquine) and whose smoking history was documented. A two-by-two table analysis was performed to compare the response rates of smokers versus nonsmokers. They found a statistically significant difference in response to antimalarials in smokers (40%) versus nonsmokers (90%).¹⁰⁸

Kreuter et al. retrospectively reviewed 36 patients with tumid lupus who were treated with antimalarials. They performed a retrospective CLASI as their outcome measure. They report that 28 of the 36 patients were current smokers (78%). The proportion of smokers in their study was much higher than expected, based on a cross-sectional analysis of an age and sex-matched population. The smokers had an increased CLASI score on presentation when compared to the nonsmokers, and had less improvement of their CLASI score during the course of therapy with antimalarials.²³

We found one case report describing clinical improvement in a patient with DLE when she decreased the amount she smoked.¹⁰⁹

CONCLUSIONS

Population studies suggest that patients with DLE are more likely to smoke than their age and sex-matched population cohorts. There is evidence suggesting that smoking decreases the efficacy of antimalarials. There are no randomized controlled trials assessing the benefit of smoking cessation on CLE.

Is Sunscreen Effective in the Treatment of Cutaneous Lupus?

We found one open-label study of the efficacy of broad-spectrum sunscreen in the treatment of CLE.¹¹⁰ Eleven patients with CLE that was inducible with photoprovocation were treated with three different commercially available sunscreens in 5 cm × 5 cm test spots, 20 minutes prior to irradiation. Photoprovocation was carried out with UVA and UVB devices. All three sunscreens prevented formation of CLE lesions within their respective 5 cm by 5 cm phototesting areas.

CONCLUSIONS

There is evidence that sunscreen use is an effective prevention measure in the development of UV-induced CLE.

Are Laser Treatments Effective in the Treatment of Cutaneous Lupus?

We found no randomized controlled trials assessing the efficacy of laser treatment in CLE.

There are three case series^{111–113} and five case reports^{114–118} assessing patient improvement after treatment with argon and pulse dye lasers. In total, 66 patients have been treated, and 44 of them were reported to have improved.

Toxicity

Pain, immediate purpura, and postinflammatory hyperpigmentation were reported as side effects of laser therapy in patients with CLE.

CONCLUSIONS

There is insufficient evidence to recommend pulse dye or argon lasers as a treatment in CLE.

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What We Know

- There are few randomized-controlled trials for the treatment of CLE.
- Systematic reviews reveal obvious benefits of antimalarials in treating SLE.
- There are no randomized placebo-controlled trials assessing the efficacy of antimalarials in the treatment of CLE; however, antimalarials are historically accepted as the first line therapy for CLE. Chloroquine may have slightly greater efficacy than hydroxychloroquine, but chloroquine is less well tolerated. Addition of quinacrine appears to be helpful for refractory patients, but is limited by side effects. There is little evidence of harm from antimalarials.
- Thalidomide has been shown, in a summation of case series, to be successful in the treatment of more than 400 patients with CLE refractory to accepted first line therapies. Randomized controlled trials are needed to better elucidate the benefits of thalidomide in CLE, particularly given the well-documented risks of this medication.
- There is good evidence supporting the use of potent topical steroids in the treatment of DLE.
- There is good evidence to support the role of topical calcineurin inhibitors in the treatment of CLE.
- There is evidence that sunscreen use is an effective prevention measure in the development of UV-induced CLE.
- Population studies suggest that patients with DLE are more likely to smoke than their age and sex-matched population cohorts. There is evidence suggesting that smoking decreases the efficacy of antimalarials.

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Treatment of Cutaneous Dermatomyositis

34

Ruth Ann Vleugels, M.D., and Jeffrey P. Callen, M.D.

INTRODUCTION

Dermatomyositis is an idiopathic inflammatory myopathy characterized by progressive proximal muscle weakness and pathognomonic or characteristic cutaneous manifestations. Management of patients with cutaneous lesions of dermatomyositis must begin with a systematic investigation for the presence of muscle disease, the presence of additional systemic involvement, particularly of the pulmonary, cardiac, and/or gastrointestinal systems, and for the possibility of an accompanying malignancy. Detection of any of these potentially associated features dictates the initial approach to disease management. Notably, management of cutaneous lesions in patients with dermatomyositis is often challenging and can require multiple sequential and/or combined therapies. Many patients with muscle and systemic disease will have continued problems with their skin, despite control of their systemic disease. Thus, the cutaneous manifestations of this disease can remain highly refractory to therapy and challenging to manage. In addition, in some patients with dermatomyositis, cutaneous disease exists in the absence of objective evidence of muscle weakness and elevated muscle-derived enzymes. These cases are referred to as amyopathic dermatomyositis and can be difficult to manage. For these reasons, the dermatologist has a unique role to play in caring for patients with this disease.

Very few prospective, randomized studies have been conducted on skin disease in dermatomyositis, requiring clinicians to rely on case reports and retrospective reviews in formulating their approach to treatment. In this chapter, we will review the evidence that exists regarding the therapeutic options for dermatomyositis, while specifically highlighting treatment options used for the cutaneous manifestations of this disease.

EPIDEMIOLOGY

A study published in 1990, by Oddis, et al. reported an incidence of dermatomyositis of 5.5 cases per million, with an increasing incidence noted over the two decades represented in the study period.¹ A recent population-based study published in 2010, found the incidence of dermatomyositis to be 9.63 per million, with an incidence of clinically amyopathic dermatomyositis of 2.08 per million.²

In addition, this study also found the incidence of dermatomyositis to be 13.98 per million in women and 4.68 per million in men, supporting previous epidemiologic data indicating that women are affected by dermatomyositis more often than men. In this population-based study, malignancy was present in 28% of participants², strengthening the best previously existing data that 18–32% of dermatomyositis patients have or will develop a malignancy.³ The incidence of the juvenile form of dermatomyositis (diagnosed up to age 16), has been estimated to be 1.9 per million, with a female-to-male ratio of 5:1, and median age of onset of 6.8 years.⁴ These patients have little to no increased risk of malignancy, but they are at an increased risk of calcinosis relative to the adult form of disease.

ETIOLOGY

Although the exact pathogenesis of dermatomyositis has yet to be elucidated, the disease is thought to result when varying factors, such as malignancy, infections, or drugs, trigger an immune-mediated process in a genetically predisposed individual.⁵ Serum antinuclear autoantibodies, as well as other myositis-specific autoantibodies, are often present. In addition, there is increasing evidence to support that autoantigens activate a humoral immune process in which complement is deposited in capillaries, resulting in capillary necrosis and ischemia.⁶ Finally, dermatomyositis is also known to be photoexacerbated.^{7–9}

DIAGNOSIS

The diagnosis of dermatomyositis often involves clinical recognition of the characteristic cutaneous manifestations along with a skin biopsy that is compatible. Cutaneous disease includes pathognomonic changes, referred to as the heliotrope eruption and Gottron's papules, as well as characteristic features, including photoexposed violaceous erythema, violaceous erythema on the extensor surfaces, malar erythema, nonscarring alopecia with or without scaly poikilodermatos changes, erythematous papules and/or plaques on the lateral thighs (Holster sign) and cuticular/periungual changes.¹⁰ Less common cutaneous lesions of dermatomyositis include mechanic's hands (hyperkeratosis of the lateral fingers and palms), panniculitis, urticaria, a flagellate erythema, follicular hyperkeratosis, erosive or

vesicobullous lesions, and an exfoliative erythroderma.³ Calcinosis and changes consistent with a cutaneous vasculopathy can also be present, particularly in cases of juvenile dermatomyositis.

Investigation for associated muscle disease and/or systemic disease is necessary in all patients, including those with no symptoms of muscle weakness or systemic involvement. Evaluation traditionally involves strength testing of the proximal muscles, serum levels of muscle-derived enzymes (creatinine kinase and aldolase), and often an electromyogram, magnetic resonance imaging study, or muscle biopsy. Investigations for interstitial lung disease (pulmonary function tests with diffusion studies and a chest x-ray or possibly a high resolution CT scan), for esophageal disease (barium swallow or manometry), and for cardiac disease (electrocardiogram), should be completed at the time of diagnosis. Additionally, the patient should undergo a systematic evaluation for an associated malignancy which is repeated annually as we have recently reviewed elsewhere.³ It is important to note, that patients with amyopathic dermatomyositis also may have an associated malignancy or may develop systemic manifestations such as fulminant pulmonary disease.¹¹ Therefore, investigations for malignancy and associated systemic disease must be conducted in this subset of patients as well.

SEARCH METHODOLOGY

A PubMed search was performed using the search term “dermatomyositis treatment AND.” Only articles available in English were included. Titles and abstracts were reviewed for relevance. References were also gathered from the cited studies and reports reviewed. Case reports and retrospective reviews were considered given the relative lack of prospective studies available on therapeutic interventions for cutaneous dermatomyositis.

RESEARCH QUESTIONS AND THEIR ANSWERS

There are multiple limitations in assessing the various therapeutic approaches to dermatomyositis. Most existing information regarding therapy for dermatomyositis is in the form of retrospective reviews. In fact, in a Cochrane review article, only four high-quality randomized controlled studies on dermatomyositis were identified, and none specifically focused on its cutaneous manifestations.¹² The low incidence of dermatomyositis, coupled with the fact that studies traditionally pooled cases of polymyositis and dermatomyositis when considering therapeutic regimens, further complicates the assessment of treatment options for this disease. In addition, given the refractory nature of the skin manifestations and the frequent association with muscle and/or systemic disease, data on true monotherapy is virtually nonexistent. Finally, until recently there were no

TABLE 34-1—Therapeutic Ladder for Cutaneous Disease in Dermatomyositis

First Line
Photoprotection including sunscreens, wide-brimmed hats, sun-protective clothing, and behavioral modification
Topical corticosteroids
Topical tacrolimus
Oral antimalarials
Combination antimalarials (hydroxychloroquine or chloroquine plus quinacrine)
Second line
Methotrexate
Mycophenolate mofetil
Intravenous immunoglobulin
Third line
Thalidomide
Dapsone
Rituximab

Adapted from Vleugels/Callen, Dermatologic Signs of Internal Disease.³

validated measures in assessing cutaneous disease severity in dermatomyositis.

Given these limitations, the purpose of this chapter is to provide care providers with the existing evidence behind various therapeutic options in order to allow more evidence-based treatment recommendations. (Please see Table 34-1 for a therapeutic ladder for cutaneous disease in dermatomyositis and Table 34-2 for existing evidence-based data for the treatment of dermatomyositis.)

Photoprotection

Studies have demonstrated that both UVA and UVB are involved in the elicitation of certain subtypes of cutaneous lupus erythematosus, and a similar phenomenon is thought to occur in dermatomyositis as well, although studies are lacking.¹³ It has been shown that patients with dermatomyositis, similar to those with lupus erythematosus, demonstrate a significantly reduced minimal erythema dose (MED) to UVB irradiation compared to healthy controls.⁸ Another study was able to reproduce skin lesions of dermatomyositis with solar-simulated radiation in 1 of 6 patients however, 5 of 10 patients indicated that light would worsen their existing cutaneous lesions.⁹

Patients should be counseled that their disease may be exacerbated by light even in very limited exposures.⁷ Given the photoexacerbated nature of dermatomyositis, year-round daily photoprotection with a broad-spectrum sunscreen with sun protective factor of at least 30 is recommended, and reapplication should occur every 3–4 hours.¹⁴ Wide-brimmed hats, sun protective clothing, and behavioral modification should also be encouraged as skin

TABLE 34-2—Existing Evidence-based Data for the Treatment of Dermatomyositis

	Muscle Disease	Cutaneous Disease
Level 1 Evidence (prospective randomized-controlled trial)	Oral corticosteroids High-dose IVIG Azathioprine In progress: rituximab, methotrexate, infliximab, etanercept, oral tacrolimus, methimazole, monoclonal antibody directed against the fifth component of complement, MEDI-545 Plasmapheresis and leukapheresis (*showing no benefit)	High-dose IVIG Plasmapheresis and leukapheresis (*showing no benefit)
Level 2 Evidence (retrospective study and/or large case series)	Low-dose methotrexate Mycophenolate mofetil Cyclosporine Cyclophosphamide Chlorambucil Rituximab	Hydroxychloroquine Low-dose methotrexate
Level 3 (small case series and/or case report/s)	Infliximab Etanercept Oral tacrolimus Sirolimus Total body irradiation Stem cell transplantation	Sunscreens Topical corticosteroids Topical tacrolimus Hydroxychloroquine or chloroquine plus quinacrine Mycophenolate mofetil Thalidomide Dapsone Adjuvant leflunomide Antiestrogen medications (tamoxifen, anastrazole) Infliximab Etanercept Efalizumab (prior to being removed from the US market in 2009) Rituximab Oral tacrolimus Sirolimus Total body irradiation Stem cell transplantation

manifestations are challenging to control without adequate photoprotection. Notably, there have been cases reported involving flares of internal disease following solar irradiation in patients with dermatomyositis, similar to this more recognized phenomenon in lupus erythematosus.⁷ Given the careful photoprotection warranted in patients with dermatomyositis, consideration should be given to vitamin D status and possible supplementation.

Anti-Pruritics

Pruritus, often a prominent feature of the skin disease of dermatomyositis, can significantly affect patients' quality of life.^{15,16} In addition, it can occasionally help clinically distinguish dermatomyositis from lupus erythematosus. Pruritus, in particular scalp pruritus, can be the initial presenting symptom in dermatomyositis. Because it can interfere with sleep patterns and overall quality of life, pruritus should be treated aggressively. Topical preparations used for symptomatic relief include topical antihistamines, pramoxine, menthol, camphor, and lidocaine.¹⁷

The addition of oral antihistamines (hydroxyzine or doxepin), amitriptyline, or other agents that can improve pruritus, and thereby quality of life, is often necessary.

Topical Corticosteroids

Topical corticosteroids of various strengths are often used to improve the pruritus and reduce the erythema associated with the cutaneous lesions of dermatomyositis.¹⁸ Class I topical corticosteroids are often employed to treat the dorsal hands, extensor surfaces, and scalp, while lower potency agents are often utilized for the heliotrope eruption and facial erythema. These topical agents can be used under occlusion for refractory hyperkeratotic lesions, particularly those on the dorsal hands.¹⁷ Intralesional corticosteroid therapy is occasionally used for refractory lesions or for the associated scalp dermatitis, however, this is often impractical given the extent of cutaneous disease.¹⁸ In many patients, photoprotection and topical agents alone are insufficient in controlling the cutaneous disease of dermatomyositis.

Topical Calcineurin Inhibitors

Given the refractory nature of skin lesions in dermatomyositis, topical agents other than corticosteroids have been tried in an attempt to improve cutaneous disease. There have been several cases and one pilot study in the literature regarding the efficacy of topical tacrolimus on skin lesions in dermatomyositis.^{19–22} Of note, in these reports, all patients were on additional therapeutic agents at the time of initiation of topical tacrolimus. In the pilot study, six patients (five adults and one juvenile dermatomyositis participant) were followed for 6–8 weeks after initiation of topical tacrolimus. Two had >90% improvement, one had 40–90% improvement, and three had 20–40% improvement during the follow-up period.²³ A side-by-side comparison in a different group of five patients, however, showed a lack of benefit with topical tacrolimus.²⁴ In a small group of pooled patients with both lupus erythematosus and dermatomyositis with facial lesions, one of the two patients with dermatomyositis had good response to topical tacrolimus, while the other did not improve with this intervention.¹⁹ Given these reports, topical tacrolimus is a reasonable agent to consider for refractory cutaneous lesions of dermatomyositis. There are currently no published reports on pimecrolimus for cutaneous dermatomyositis, however, the authors have anecdotally noted some limited success in patients using this cream.

Antimalarials

Antimalarials have been used in the treatment of the cutaneous disease associated with dermatomyositis for over 50 years. Traditionally, mepacrine was used as a first line agent, however given its increased risk of diplopia; a shift was made to the use of other antimalarials.

Although chloroquine and related antimalarials have been reported to be effective as first-line therapy in the treatment of the cutaneous manifestations of dermatomyositis, they are seemingly not beneficial for the associated muscle disease.²⁵ The lack of effect of hydroxychloroquine on muscle disease suggests that the beneficial effects of this medication on the skin may be a result of photoprotection rather than systemic immunomodulation, or that the pathogenetic mechanisms involved in dermatomyositis differ in skin and muscle disease, a concept supported by a study published in the *Lancet* in 2003.^{6,18}

Hydroxychloroquine in doses of 200–400 mg/day is effective in up to 75% of patients in partially or completely controlling the cutaneous disease and allowing a decrease in corticosteroid dosage. In an open study of seven dermatomyositis patients with cutaneous lesions that had not responded to topical therapy, the addition of hydroxychloroquine resulted in improvement in all seven patients, with total resolution of skin lesions in three patients and tapering of corticosteroid dosage in two patients.²⁶ Additional small studies similarly demonstrated favorable results with hydroxychloroquine used for cutaneous disease in adult

patients, including those with amyopathic dermatomyositis, and in pediatric patients with dermatomyositis.^{27–30} In one pediatric study, however, three of nine patients developed ocular side effects that mandated discontinuation of hydroxychloroquine.³⁰ In addition, another report indicated worsening of rash in two children with dermatomyositis after the initiation of hydroxychloroquine.³¹

It has been reported that patients with dermatomyositis have an increased risk of developing morbilliform drug reactions from hydroxychloroquine, and counseling patients regarding this possibility prior to initiation of therapy is helpful.³² Development of a morbilliform eruption often mandates discontinuation of hydroxychloroquine given that dermatomyositis skin disease has been noted to koebnerize in this situation. Counseling patients regarding smoking cessation is also essential as the efficacy of hydroxychloroquine appears to be reduced in patients who smoke.

Patients who lack adequate response to hydroxychloroquine can be switched to chloroquine therapy 250–500 mg/day, or can receive quinacrine 100 mg once or twice daily in addition to either hydroxychloroquine or chloroquine. Chloroquine is used more frequently than hydroxychloroquine in Europe given possible increased efficacy. It does, however, carry an increased risk of irreversible retinopathy and is therefore used less often than hydroxychloroquine in the United States. Quinacrine may be used as add-on therapy in conjunction with either hydroxychloroquine or chloroquine given that it lacks ocular toxicity (hydroxychloroquine and chloroquine should never be prescribed in combination given possible additive ocular toxicity). Quinacrine may not be readily available in all locations, however, and must be obtained at special compounding pharmacies. One published report has supported the synergistic effect of combination antimalarials in cutaneous dermatomyositis.³³ In this retrospective case series, 7 of 17 patients experienced at least near clearance in cutaneous disease with the use of antimalarial therapy alone (3 responded to antimalarial monotherapy while 4 required combination therapy of hydroxychloroquine-quinacrine or chloroquine-quinacrine). These findings suggested that a significant subset of patients might benefit from combination antimalarial therapy when antimalarial monotherapy has been ineffective.

Conventional precautions regarding antimalarial therapy should be taken, including a careful ophthalmologic examination prior to or within several months of initiation of therapy and annually thereafter in follow-up.³⁴ Quinacrine therapy requires blood count monitoring given the rare potential risk of associated aplastic anemia. Quinacrine can also cause gastrointestinal upset as well as a reversible yellow discoloration of the skin.

Corticosteroids

The mainstay of initial therapy for active muscle or systemic disease in dermatomyositis is the use of high-dose systemic

corticosteroids. Traditionally, prednisone is given in a dose of 0.5–1.5, mg/kg/day (maximum daily dose of 60 mg) as initial therapy.³⁵ Systemic corticosteroid treatment should continue at these doses for at least 1 month after the myositis has become both clinically and enzymatically inactive. At this point, the dose can be tapered slowly, generally over a period lasting 1.5 to two times as long as the period of active treatment.

It is crucial to emphasize that a slow taper of corticosteroids is necessary to prevent relapse of active disease. A dermatology-based case series supported the hypothesis that a significant number of patients (75–85%) can become muscle disease-free, off treatment, after a period of 2–4 years, utilizing a slow corticosteroid taper.²⁹ Long-term follow-up of cases of juvenile dermatomyositis also supported this conclusion.^{36,37} Despite these reports, there have been no controlled long-term studies assessing whether patients with dermatomyositis, unlike those with systemic lupus erythematosus, can achieve long-term remission off therapy.³⁸ In addition, there are no randomized controlled studies comparing various corticosteroid doses or taper rates in patients with dermatomyositis.

Intravenous pulse methylprednisolone has been used in multiple studies, both in adult and juvenile cases of dermatomyositis, most with favorable results.^{39–45} It may be most beneficial in rapid control of a fulminant disease process, usually myositis or pulmonary disease, associated with dermatomyositis.

There is known to be a discordant response to therapy between muscle and skin disease in dermatomyositis.²⁹ Even after the myositis and systemic disease are controlled, the cutaneous disease often remains recalcitrant to therapy and can be particularly challenging to manage. For these reasons, there are subsets of patients in which cutaneous disease becomes the primary component of disease management. This includes patients with postmyopathic dermatomyositis (patients with adequately treated muscle disease who continue to have active cutaneous disease),¹⁷ and those with clinically amyopathic dermatomyositis. In both of these subsets of patients, which lack active myositis, aggressive corticosteroid therapy is frequently not warranted.

Anecdotal experience supports the concept that systemic corticosteroids have varying degrees of efficacy for the cutaneous manifestations of dermatomyositis, with only a small subgroup of patients having excellent responses at doses that do not cause toxicity. In addition, many patients on toxic doses of systemic corticosteroids have little to no effect on their cutaneous disease or its associated symptoms. Therefore, treatment of amyopathic and postmyopathic dermatomyositis often differs significantly from that of classic dermatomyositis. In sum, given the host of potential side effects of long-term systemic corticosteroid therapy as well as the refractory nature of the skin lesions in dermatomyositis, systemic corticosteroids are not considered the mainstay in therapy for cutaneous disease.

Methotrexate

Approximately 25–43% of patients with dermatomyositis have muscle disease that will not respond to systemic corticosteroids or develop significant steroid-related side effects.^{46,47} In these patients, immunosuppressive agents may be necessary to induce or maintain disease remission.

Methotrexate is traditionally administered in an empiric dose of 25–50 mg/week for the muscle disease of dermatomyositis. Methotrexate is often used as add-on or alternative therapy when corticosteroids alone fail. It also is frequently used as a first-line agent in combination with prednisone. It can be used on a weekly basis, given either orally, intramuscularly, subcutaneously, or intravenously. The drug usually becomes effective in 4–8 weeks, and therefore is not recommended for rapid control of a fulminant disease process. In patients requiring adjunctive therapy, methotrexate induces response rates of 70–77%.^{46,48,49} Patients with juvenile dermatomyositis have also improved with methotrexate,^{50–54} with some also demonstrating steroid-sparing.⁵⁰

No randomized controlled study has been performed comparing methotrexate in combination with prednisone versus prednisone alone. There has been a double-blind, randomized controlled trial comparing methotrexate and azathioprine in a pooled group of dermatomyositis and polymyositis participants.⁵⁵ In this trial, efficacy was similar for both drugs, however methotrexate resulted in fewer side effects. In addition, another study demonstrated better response of myositis to methotrexate than to azathioprine in a group of patients with dermatomyositis, polymyositis, and inclusion body myositis.⁴⁸ Finally, a randomized cross-over study demonstrated a trend in favor of oral methotrexate combined with oral azathioprine over intravenous methotrexate in 30 patients with both dermatomyositis and polymyositis.⁵⁶

Retrospective reviews and open-label studies support the usefulness of methotrexate in doses between 10 and 40 mg/week specifically for the cutaneous manifestations of dermatomyositis. In a review of 22 patients treated with combined methotrexate and systemic corticosteroid therapy, 17 patients improved on methotrexate resulting in steroid-sparing.⁴⁹ Another review of 13 patients with little to no muscle involvement treated with 2.5–30 mg/week of methotrexate for refractory cutaneous dermatomyositis, demonstrated complete clearance in four patients, near complete clearance in four patients, and moderate clearance in all remaining patients. In addition, dose reduction and/or discontinuation of other therapies was facilitated.⁵⁷ There has also been demonstrated benefit for skin disease in juvenile dermatomyositis with the prevention of calcinosis formation. In one study, 12 pediatric patients with severe disease were treated with intravenous methylprednisolone in conjunction with methotrexate. Two of the six patients who initiated therapy greater than 5 months after diagnosis developed calcinosis, whereas none of the six patients treated within 6 weeks of diagnosis developed calcinosis.⁴³

Despite numerous reports indicating the potential efficacy of methotrexate, adverse effects including both liver and pulmonary toxicity must be considered. In one retrospective study, ten patients with dermatomyositis (7 with classic dermatomyositis and 3 with amyopathic disease) were treated with methotrexate. Improvement of cutaneous disease occurred in seven (100%) of the patients with classic dermatomyositis and in two (66%) of those with amyopathic dermatomyositis, while myositis improved in four (57%) of the seven patients with muscle disease. Systemic steroid-sparing was also enabled. Despite improvement in their disease, methotrexate-related side effects occurred in seven of the ten patients (in six patients with classic dermatomyositis and in one patient with amyopathic dermatomyositis). Of the four patients that underwent liver biopsy, two demonstrated mild hepatic fibrosis resulting in discontinuation of methotrexate. Notably, both patients with hepatic fibrosis on biopsy had preexisting steroid-induced diabetes mellitus.⁵⁸

In sum, both the myositis and cutaneous disease of dermatomyositis have demonstrated response to methotrexate. In fact, methotrexate is often considered first-line as a steroid-sparing agent in dermatomyositis although careful patient selection and monitoring for side effects is essential.

Azathioprine

Azathioprine is administered orally in doses of 1–2 mg/kg/day depending on results of thiopurine methyl transferase (TPMT) enzyme testing in order to achieve efficacy yet avoid bone marrow suppression. There has been a randomized-controlled trial comparing prednisone plus azathioprine to prednisone plus placebo for the muscle disease of polymyositis. Although there were no statistically significant differences between the two groups at three months, in the open follow-up period at 3 years, patients treated with azathioprine had greater muscle strength and required a significantly lower steroid dosage.⁵⁹ Given the now better-recognized differences in pathogenetic mechanisms for dermatomyositis and polymyositis, it is unclear how much scientific relevance this study has on dermatomyositis patients with muscle disease.

As noted in the section on methotrexate, there has also been a randomized controlled trial comparing azathioprine and methotrexate in patients with both dermatomyositis and polymyositis. Although efficacy of both agents was similar, azathioprine caused more side effects in this study.⁵⁵ Also, in a pooled group of patients with idiopathic inflammatory myopathies, methotrexate resulted in better response in muscle disease than azathioprine.⁴⁸ Given this data, azathioprine is often considered second line, after methotrexate, for the muscle disease of dermatomyositis.

There is less data for the use of azathioprine in juvenile dermatomyositis, however, steroid-sparing has been demonstrated in some pediatric cases.⁴⁷ Experience with

azathioprine and cutaneous disease in dermatomyositis is anecdotal, but does suggest that some patients respond to azathioprine resulting in steroid-sparing effects.

Mycophenolate Mofetil

Mycophenolate mofetil has been shown to be an effective therapeutic option for control of muscle disease in dermatomyositis.^{60–63} One series demonstrated both efficacy and steroid-sparing, however, also noted that opportunistic infections developed in three of ten patients.⁶¹ Retrospective reviews and open-label studies also support the efficacy of mycophenolate mofetil for the cutaneous disease of DM.^{62,64,65} One series of four cases demonstrated improvement in patients with refractory skin disease that had failed to respond to systemic corticosteroids, hydroxychloroquine, and/or methotrexate.⁶⁴ Another retrospective review of the effectiveness of mycophenolate mofetil in patients with refractory cutaneous dermatomyositis found improvement in 10 of 12 patients at doses of 500 mg to 1 g twice a day. In this review, most patients tolerated mycophenolate mofetil without side effects; however, one patient developed a central nervous system B-cell lymphoma and another developed elevated liver function tests and urinary symptoms. These side effects resolved upon discontinuation of mycophenolate mofetil in both cases.⁶⁵

Cyclosporine

Several studies have supported the use of cyclosporine in both adults and children as a steroid-sparing agent to control either muscle or lung disease in dermatomyositis.^{66–72} In one prospective study, ten patients with dermatomyositis who received cyclosporine achieved remission more quickly than controls.⁶⁷ Cyclosporine plus prednisone has been compared to methotrexate plus prednisone in a randomized controlled fashion for the muscle disease of both dermatomyositis and polymyositis.⁶⁹ Both groups improved on therapy, and patients treated with methotrexate demonstrated a mildly improved response compared to patients treated with cyclosporine, however, this difference was not statistically significant. Cyclosporine should be considered for rapidly progressive interstitial lung disease (ILD) associated with dermatomyositis. Once patients have developed respiratory failure, however, cyclosporine is ineffective.^{73,74}

In terms of its use for the cutaneous disease of dermatomyositis, there is a report of refractory skin necrosis responding to cyclosporine.⁷⁵ Other than this report, however, experience with cyclosporine for the skin manifestations of dermatomyositis is anecdotal.

Tacrolimus

Oral tacrolimus (FK-506) has been reported to be effective in the treatment of refractory ILD associated with

dermatomyositis (both classic and amyopathic) and polymyositis.^{76–79} In these reports, patients had progressive disease despite conventional therapies, such as high-dose corticosteroids, cyclosporine, and/or pulse cyclophosphamide, yet improved clinically with oral tacrolimus. In the largest series of adult patients with anti-aminoacyl-transfer RNA synthetase (anti-aaRS)-associated ILD and idiopathic inflammatory myopathy, all 13 had improvement of their pulmonary disease, while 10 had improvement in muscle disease as well.⁷⁸ Despite these results, there was no data provided from this series on the effect of oral tacrolimus on skin disease. Additional reports have specifically highlighted improvement in muscle disease recalcitrant to other therapies on oral tacrolimus.^{77,80}

Although reports in adults are lacking, several cases have demonstrated improvement of skin disease in children with juvenile dermatomyositis treated with oral tacrolimus.^{81–83} Myositis also responded to oral tacrolimus in some of these reports, while demonstrating lack of response in others.

Chlorambucil

When used alone or in conjunction with other agents, chlorambucil has demonstrated benefit on the muscle disease of dermatomyositis in case reports.^{84–86} However, these reports noted either little or no improvement in cutaneous disease with this medication.

Cyclophosphamide

Multiple reports have demonstrated improvement in the ILD associated with dermatomyositis on cyclophosphamide, particularly fulminant or rapidly progressive lung disease.^{87–90} In terms of its effects on the skin manifestations of dermatomyositis, there has been one case of refractory cutaneous vasculitis resulting in ulcers that responded completely to repeated intravenous cyclophosphamide pulse therapy without adjunctive high-dose corticosteroids. Repeat biopsy after treatment with cyclophosphamide confirmed complete remission of vasculitis, and no adverse effects were noted in the patient.⁹¹

Dapsone

Oral dapsone has shown to be beneficial in refractory cutaneous dermatomyositis in case reports and a small series.^{92,93} In the series of two patients with cutaneous dermatomyositis unresponsive to combination therapy with prednisone, hydroxychloroquine, quinacrine, and immunosuppressive medications, both had rapid improvement in cutaneous disease with the addition of dapsone to their therapeutic regimens. Both patients also experienced exacerbation of their skin disease after discontinuation of dapsone as well as subsequent improvement after reinitiation of this medication.⁹³ Other reports, one involving a case of drug-induced amyopathic dermatomyositis⁹⁴ and

another a case of postmyopathic dermatomyositis with residual cutaneous disease,⁹⁵ did not respond to dapsone.

Thalidomide

Cutaneous dermatomyositis recalcitrant to other therapies has anecdotally responded to thalidomide.⁹⁶ In addition, the case of drug-induced amyopathic dermatomyositis mentioned above, which was unresponsive to dapsone as well as oral corticosteroids, antimalarials, and methotrexate, was treated with initial marked success with thalidomide; however, no long-term follow-up was provided.⁹⁴

Intravenous Immunoglobulin

There are numerous cases in which the muscle disease of the idiopathic inflammatory myopathies has responded to intravenous immunoglobulin (IVIG).^{97–100} In a retrospective study, patients treated with prednisone, cyclosporine, plus IVIG had an increased remission rate when compared to patients treated with prednisone and cyclosporine alone.¹⁰¹ IVIG was also demonstrated to be a safe and effective steroid-sparing agent when added on to mycophenolate mofetil for severe and refractory myositis in another retrospective study.¹⁰² In addition, a small series highlighted potential efficacy in ILD associated with dermatomyositis, with improvement demonstrated in two of five patients.¹⁰³ Several reports and series have demonstrated benefit in cases of juvenile dermatomyositis as well,^{97,104–107} including in a subset of children who had never received systemic corticosteroids.¹⁰⁸ Recently, an ad hoc committee of the American Association of Neuromuscular and Electrodiagnostic Medicine (AANEM) considered the rational use of IVIG for various neuromuscular disorders. Class evidence I, the strongest category, was found to support the use of IVIG for dermatomyositis.¹⁰⁹

It has been reported that patients with amyopathic dermatomyositis may respond to one-tenth the usual dose of IVIG.¹¹⁰ There has also been a case described of cutaneous disease refractory to prednisone, methotrexate, and hydroxychloroquine that responded to IVIG. In this case, new cutaneous ulcerations stopped developing 1–2 weeks after initiation of IVIG therapy.¹¹¹

Unlike for many agents in dermatomyositis, the efficacy of high-dose IVIG has been investigated in a randomized, placebo-controlled clinical trial.¹¹² In this trial, fifteen patients were dosed with 2 gm/kg of IVIG versus placebo monthly for 3 consecutive months with the option of crossover for an additional 3 months. Of the 11 patients receiving placebo, none had major improvement, three had mild improvement, three had no change, and five had disease worsening, whereas nine of 12 patients who received IVIG after crossovers had major improvement with near return to normal function. Those patients who received IVIG also had improvement in their cutaneous disease. Despite these promising results, the improvement

in strength noted with IVIG often lasts for only 1–2 months, indicating that IVIG therapy may need to be continued for longer-term effects.¹¹³ Although ongoing therapy is often beneficial, the high cost of this therapeutic intervention can present a challenge.

Not all studies involving IVIG and its effect on dermatomyositis have demonstrated favorable outcomes. In fact, one study of high-dose IVIG on molecular expression in muscle tissue of patients with inflammatory myopathies demonstrated limited benefit.¹¹⁴ In this pooled study of 13 patients with idiopathic inflammatory myopathy, five had either adult or juvenile dermatomyositis. Three of these five patients demonstrated dramatic improvement in cutaneous disease with IVIG. In terms of muscle disease, however, serum creatine kinase (CK) levels decreased significantly in only five of the 13 patients. In addition, only three of the thirteen patients improved their Functional Index (FI) in Myositis score by greater than 20%. Therefore, clinical improvement based on FI score was limited although statistically significant. Although some patients in this study demonstrated either clinical improvement or decreased serum CK levels, there was no significant improvement of inflammation in muscle tissue based on numbers of T-cells or macrophages, expression of MHC class I and II antigen on muscle fibers, or endothelial cell activation.¹¹⁴ In spite of these results, which call into question the role of high-dose IVIG as an immune-modulating therapy for idiopathic inflammatory myopathy, IVIG remains the only therapeutic agent that has demonstrated beneficial results in the treatment of cutaneous dermatomyositis in a randomized-controlled trial.

PLASMAPHERESIS AND LEUKAPHERESIS

A placebo-controlled study has demonstrated that plasmapheresis and leukapheresis are no more effective than sham apheresis in corticosteroid-resistant dermatomyositis.¹¹⁵ Despite significant reductions in the levels of serum muscle enzymes with plasma exchange, no significant differences were found in either the final muscle strength or the functional capacity of the patient groups in the trial. This study also demonstrated no benefit in muscle strength or functional capacity from leukapheresis despite significant decreases in lymphocyte counts.

Another study found that plasmapheresis did not offer any advantage to patients being treated with other immunosuppressive medications.¹⁰¹ Although the main finding of this study was that patients receiving prednisone, cyclosporine, plus intravenous immunoglobulin had a significantly higher probability of maintaining complete remission at the end of a 4-year follow-up period than those treated with prednisone and cyclosporine alone, the authors also noted that there was no additional benefit observed from the addition of plasma exchange in these patients. In sum, plasmapheresis and leukapheresis are not considered effective therapeutic options for dermatomyositis.

ANTI-TUMOR NECROSIS FACTOR-ALPHA MEDICATIONS

Numerous case reports have indicated benefits from anti-tumor necrosis factor-alpha (TNF-alpha) medications on both refractory adult and juvenile dermatomyositis.^{116–126} Although most of these reports focus on the myositis component of disease, several also report improvement in cutaneous disease on anti-TNF-alpha therapy.^{117,123,124,126}

Despite numerous beneficial case reports, a pilot study of infliximab for patients with refractory idiopathic inflammatory myopathies demonstrated both radiologic and clinical worsening of muscle disease, as well as activation of the type I interferon system in several cases.¹²⁷ In addition, a series of patients with dermatomyositis treated with etanercept all had worsening of muscle disease.¹²⁸ Finally, an open-label trial of weekly methotrexate plus infliximab in new-onset dermatomyositis and polymyositis was terminated prematurely because of a high drop-out rate secondary to disease progression and infusion reactions in some participants, as well as an overall low inclusion rate.¹²⁹ The few patients who remained in the study until a primary endpoint did have improvement in muscle disease activity and serum CK levels.

In addition to the concern of exacerbating a patient's myositis with anti-TNF-alpha therapy, there have also been cases reporting the development of dermatomyositis-like cutaneous eruptions in patients on anti-TNF medications for other diseases such as rheumatoid arthritis.¹³⁰ One report also details the onset of dermatomyositis, with muscular, pulmonary, and mild cutaneous changes, occurring in a patient being treated with etanercept for seronegative rheumatoid arthritis.¹³¹

Efalizumab

Efalizumab has been reported to be of benefit in one case of refractory dermatomyositis.¹³² After failing to improve on methotrexate and prednisolone, the patient in this report had improved skin disease after being started on efalizumab 1 mg/kg/week combined with prednisolone 40 mg/day. In particular, the patient had decreased facial edema and upper chest erythema, whereas the erythematous-violaceous discoloration on the upper lids demonstrated only modest improvement. After 1 month on this therapy, the patient was also started on azathioprine 50 mg/day, along with a dose increase of efalizumab to 1.8 mg/kg/week and a dose reduction of prednisolone to 10 mg/day. At 1 year of follow-up, this patient was still doing well clinically. Efalizumab was removed from the market in the United States in the spring of 2009, for a potential increased risk of the demyelinating disease progressive multifocal leukoencephalopathy (PML), and is therefore no longer available as a therapeutic option for dermatomyositis.

Adjuvant Leflunomide

Case reports have demonstrated improvement in muscle disease in patients on leflunomide for polymyositis or dermatomyositis.^{133,134} More recently, a small case series demonstrated improvement in the cutaneous manifestations of dermatomyositis with adjuvant leflunomide in three patients refractory to multiple other systemic therapies.⁹⁵

Rituximab

A national randomized, placebo-controlled trial of rituximab for inflammatory myopathy (RIM) is currently underway. Until these results become available, clinicians must rely on the somewhat contradictory information available in case reports and three open studies utilizing rituximab for dermatomyositis.

Many case reports have shown improvement in the muscle, pulmonary, cardiac, and/or skin manifestations of dermatomyositis with rituximab.¹³⁵⁻¹⁴² One case demonstrated remission of both myositis and cutaneous disease for over 4 years.¹⁴² A series of three patients with postmyopathic disease, all with adequate control of their muscle disease on other systemic agents, utilized rituximab for deteriorating skin disease specifically.¹⁴³ Skin disease improved in all three patients in this series following rituximab. In particular, the heliotrope eruption and violaceous poikiloderma were the cutaneous manifestations of dermatomyositis that responded most effectively to rituximab. Benefit from rituximab was also reported in an open-pilot study of six patients with dermatomyositis.¹⁴⁴ In this study, patients had increased muscle strength, decreased muscle enzymes, improved forced vital capacity in three patients with ILD, and improved skin disease in all patients including hair regrowth in two patients with alopecia.¹⁴⁴

Despite the promising results of these cases and open-pilot study, the largest open trial to date of rituximab for dermatomyositis demonstrated modest improvement of muscle disease but limited effects on cutaneous disease.¹⁴⁵ Of the eight patients enrolled in this trial, three achieved partial remission, defined by a reduction in muscle deficit by at least 50% at week 24. All patients demonstrated sustained depletion of peripheral B-cells on rituximab, however, serum muscle enzyme levels and skin scores using the Dermatomyositis Skin Severity Index (DSSI) at week 24 were not significantly changed from those at baseline.

Another group of eight patients with presumed idiopathic inflammatory myopathy were also treated with rituximab, five in an open label trial, and three based on perceived medical need.¹⁴⁶ Within this group, an interesting subset of two patients with Jo-1 antibody-positive dermatomyositis demonstrated improved clinical response in myositis, as well as greater than 30% percent

improvement in serum CK levels. One of the two patients had normalized serum CK levels for 10 months, while the other had both normalized CK levels and stable pulmonary function tests for 3 years. In both patients, Jo-1 antibody levels fell modestly yet remained detectable.

In a retrospective review of four cases of juvenile dermatomyositis treated with rituximab, three patients, including one with positive myositis-specific antibody Mi-2 and two without positive myositis antibodies, improved following rituximab, while one patient failed to improve and went on to develop cutaneous vasculitis and ILD requiring cyclophosphamide.¹⁴⁷ In all three pediatric patients who responded to rituximab, improvements in both muscle and cutaneous disease were specifically noted and steroid-sparing was enabled.

Sirolimus

In the first case report utilizing sirolimus (rapamycin) in a patient with dermatomyositis, improvement was noted in both cutaneous and muscle disease within 4 weeks of initiating therapy and steroid-sparing ensued.¹⁴⁸ Although hypertriglyceridemia resulted in discontinuation of sirolimus after 3 months of therapy, the patient did not have worsening of skin or muscle disease for at least 4 months after discontinuing this therapy. Another case involved a patient with a history of refractory dermatomyositis who also underwent kidney transplantation for autosomal-dominant polycystic kidney disease. This report demonstrated benefit in using a combination of rituximab and sirolimus to not only treat the patient's posttransplant lymphoproliferative disorder, but also to maintain remission of the patient's dermatomyositis.¹⁴⁰

ANTIESTROGEN MEDICATIONS

The antiestrogen medications tamoxifen and anastrazole have been reported to improve the cutaneous manifestations of dermatomyositis in two patients. In addition, one of these patients had exacerbation of skin disease after tamoxifen was discontinued. One mechanism proposed for this improvement in skin disease on antiestrogen therapy is that tamoxifen has been found to have anti-TNF-alpha properties, and other therapies that down-regulate TNF-alpha have also previously demonstrated benefit in dermatomyositis in some cases.¹⁴⁹

TOTAL BODY IRRADIATION

Two patients with recalcitrant dermatomyositis were treated with 150 rad of total body irradiation over a 5-week period.¹⁵⁰ Both had rapid improvement in myositis with minimal side effects and remained in remission at 18 and 42 months after treatment. In addition, improvement in skin disease was also noted in both patients.

STEM CELL TRANSPLANTATION

There are increasing reports in the literature of the use of hematopoietic stem cell transplantation (HSCT) in the treatment of severe and refractory autoimmune diseases, including dermatomyositis.^{151–157} Although no data specific to patients with dermatomyositis exists, there is compiled data for HSCT for autoimmune diseases. Data from this pooled population indicated a long-lasting improvement off of immunosuppression in approximately half of patients who underwent HSCT for a severe and progressive autoimmune disease.¹⁵¹ All cases were refractory, having failed multiple systemic medications prior to HSCT. Of note, mortality related to HSCT has decreased in the past several years given improved initial patient selection and the use of better-tolerated conditioning regimens. Allogenic transplants are associated with increased morbidity and mortality, making autologous HSCT the preferred choice over allogenic HSCT when possible.¹⁵¹

With respect to dermatomyositis specifically, two adult patients with amyopathic dermatomyositis and associated refractory and progressive interstitial lung disease benefited from HSCT.^{154,156} A case of recalcitrant juvenile dermatomyositis in a preschool-aged child treated with HSCT has also been reported with improvement of both skin and muscle disease.¹⁵⁵ Two additional cases of refractory juvenile dermatomyositis in wheelchair-bound patients with contractures demonstrated dramatic improvement, including resolution of contractures, and sustained remission after autologous stem cell transplantation.¹⁵⁷ In one of these cases, there was no improvement in the child's skin disease after HSCT, while the other case does not specifically comment on the patient's cutaneous manifestations.

THERAPY FOR CALCINOSIS

Calcinosis associated with dermatomyositis can be particularly challenging to manage, particularly in cases of juvenile dermatomyositis in which calcinosis is more commonly associated than in adult dermatomyositis. Various therapies have been tried for calcinosis in the setting of dermatomyositis, including low-dose warfarin, colchicine, probenecid, diltiazem, aluminum hydroxide, alendronate, intravenous methylprednisolone, surgical excision, and electric shock wave lithotripsy (ESWL).^{158–169} Infliximab was beneficial in some patients with juvenile dermatomyositis and calcinosis in one study as well.¹²² Despite IVIG showing benefit in cases of calcinosis associated with connective tissue disease,¹⁷⁰ as well as specifically with dermatomyositis,^{170,171} another report describes two patients with dermatomyositis and progressive, extensive calcification despite several years of IVIG therapy.¹⁷² A child with debilitating contractures as well as calcifications demonstrated resolution of both following HSCT.¹⁵⁷

As mentioned above, cutaneous calcinosis can be particularly problematic in cases of juvenile dermatomyositis

and affects 29% to 70% of children with this disease.^{36,173,174} In children, aggressive and early intervention with systemic therapy seems to decrease the risk of development of calcinosis.^{36,43,167,175–178} Early aggressive therapy is often warranted in juvenile dermatomyositis given that another retrospective study demonstrated improved outcomes and sustained remission of disease in children treated with this approach.¹⁰⁷

EXERCISE AND REHABILITATION

The role of exercise and rehabilitation in the therapeutic regimen for patients with dermatomyositis should not be underestimated. Even in patients responding to pharmacologic interventions for myositis, a majority develop sustained disability.¹⁷⁹ Studies demonstrate that patients with inflammatory muscle disease who participate in exercise and rehabilitation programs have improved muscle strength and endurance, note reduced disease activity, and tolerate intensive resistance training.^{179–186} In addition, improvement in strength from using exercise regimens has been demonstrated even in the course of active disease, rather than inducing flares in muscle involvement.¹⁸⁴ In a study of children with juvenile dermatomyositis, muscle inflammation did not worsen after a single bout of exercise, suggesting that moderate exercise training is safe for patients with juvenile dermatomyositis as well.¹⁸⁷

HEALTH MAINTENANCE

In both adults and children, attention to general health maintenance principles and osteoporosis prevention is a key element of patient management. This can be accomplished by joint longitudinal care with an internist or pediatrician. In addition, adult patients with dermatomyositis should undergo rigorous malignancy screening annually for at least 3 to 5 years.

Children with juvenile dermatomyositis should be monitored by a pediatrician comfortable with monitoring their developmental milestones while on immunosuppressive therapy. Of note, lipodystrophy and metabolic abnormalities, including hypertriglyceridemia and insulin resistance, are increasingly being recognized as potential complications of juvenile dermatomyositis, and these metabolic derangements should be routinely screened for in pediatric patients with this disease.^{188,189}

CONCLUSIONS

Care providers face numerous challenges in selecting a therapeutic strategy for patients with dermatomyositis. Disease incidence is low and well-designed controlled clinical trials are relatively lacking. In addition, therapies that may prove effective in controlling a patient's myositis and/or systemic disease may make little to no impact

What We Know

- Dermatomyositis, particularly the cutaneous disease, is often refractory to therapy and can require multiple simultaneous or sequential therapeutic interventions.
- All patients presenting with dermatomyositis skin disease should undergo appropriate investigations for potential concomitant muscle disease, systemic involvement, and/or malignancy.
- Myositis and/or systemic involvement in dermatomyositis are traditionally treated with high-dose systemic corticosteroids plus/minus corticosteroid-sparing agents such as methotrexate, mycophenolate mofetil, azathioprine, or intravenous immunoglobulin, among others.
- Cutaneous disease mandates strict photoprotection and often requires topical corticosteroids. First-line systemic therapy is traditionally hydroxychloroquine. Add-on therapeutic options include quinacrine, methotrexate, mycophenolate mofetil, intravenous immunoglobulin, or thalidomide, among others.
- Most data regarding therapy for cutaneous dermatomyositis is in the form of small case series or retrospective reviews, however, well-designed, multicenter randomized controlled trials are necessary to better assess the effectiveness of therapeutic options for skin disease in dermatomyositis.

on their cutaneous disease, which is known to often be refractory and challenging to manage. Despite these limitations, care providers, particularly dermatologists, have a significant role to play in treating this patient population and improving their overall quality of life. A multidisciplinary approach should be utilized in caring for patients with dermatomyositis, and therapeutic selection should be made only after careful consideration of a patient's comorbidities, disease severity, presence of systemic involvement, and search for a potentially associated malignancy.

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Treatment of Systemic Sclerosis

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INTRODUCTION

Systemic sclerosis (SSc) is a heterogeneous disease, which can affect multiple internal organs and lead to extensive cutaneous changes secondary to excess collagen and extracellular matrix deposition. Disease pathogenesis is multifactorial, including processes of vasculopathy, autoimmunity, and tissue fibrosis.¹ More extensive skin involvement is associated with poorer prognosis and, eventually, fibrosis of the skin, internal organs, and muscles can occur.² The natural course of scleroderma is highly variable as some patients improve spontaneously while others experience a progressive disease course. Skin involvement in SSc represents a therapeutic challenge as differing therapies attempt to target the inflammation, vascular changes and/or fibrosis implicated in the pathogenesis. Treatment options are currently limited and there is a need to develop new and effective therapies applicable for patients with SSc experiencing various degrees of cutaneous involvement.

Interpretation of data from clinical trials evaluating therapies for SSc is difficult because of the small numbers of patients and variable disease course among patients. Scleroderma is a rare disease and there is difficulty in obtaining adequate numbers of patients in order to achieve statistical power to demonstrate statistically significant results. Furthermore, while some patients experience a gradual progression in their skin disease, many others spontaneously improve. Thus, a significant placebo response is often seen and limits the statistical power for studies with drugs that might have only modest efficacy. Additionally, the appropriate disease marker to examine is unclear, as it is generally believed that clinical changes of thickening in the skin are downstream and later sequelae of cutaneous disease activity, and thus might not be readily reversible with therapy. In addition, even the clinical skin changes are multiple and involve skin thickening, tightening, fibrosis tethering, and atrophy. It is difficult to find a clinical measure that is able to distinguish between these findings.

METHODS

In this chapter, we present the evidence for a variety of therapies in the treatment of the cutaneous manifestations

of SSc. Only cutaneous sclerosis and digital ulcerations are considered here, while other cutaneous manifestations associated with scleroderma such as calcinosis, telangiectasias and pigmentary changes will not be discussed. Other manifestations of SSc including Raynaud phenomenon, pulmonary arterial hypertension, interstitial lung disease, and scleroderma renal crisis are not considered here, as they are generally not addressed by the dermatologist. This review addresses therapies for systemic sclerosis and not localized scleroderma (morphea). Medline database was searched for the terms 'systemic sclerosis'. Only the highest level of evidence data was considered and reviewed for a particular treatment modality.

ENDPOINTS

Measurements of skin involvement in SSc vary and differing techniques specifically measure different aspects of skin involvement. Currently, the modified Rodnan skin score is considered the most important, reliable and validated measure for measurement of dermal thickness. The modified Rodnan skin score has shown responsiveness to change in multicenter trials and demonstrates good interobserver reliability.^{3,4} This technique is an assessment of skin thickness in 17 or 22 body areas depending on the specific modifications used. A scale of 0-3 is utilized in which 0 = normal, 1 = mild skin thickness, 2 = moderate skin thickness and 3 = severe skin thickness. There is some concern that this technique is not sensitive enough to detect small but clinically meaningful changes, and that it accounts only for skin thickness as opposed to induration or tethering of skin.⁵

Other techniques are used less frequently than the modified Rodnan skin score but may represent useful measures of cutaneous involvement in SSc. The UCLA skin score is another skin assessment where 10 specific sites are measured, with a maximum score of 3 for tethering evaluated at each site.⁶ Durometry is a validated technique with good inter- and intraobserver reproducibility which measures skin induration and correlates well with ultrasound measured thickness and modified Rodnan skin score.^{7,8} Ultrasound using a 20-30 MHz probe is another valid and reproducible technique utilized to measure dermal

thickness.⁹ The plicometer measures thickness of cutaneous plica, folded areas of skin. Additional measurement devices include an elastometer to measure lineal extension and twistometer to measure skin rotation. Such techniques warrant further validation in multicenter trials.

The aforementioned techniques are used as measures of cutaneous involvement in SSc and utilized to measure improvement with investigational agents in clinical trials. Although controlled trials generally report statistically significant changes in such disease measures, the minimally important difference (MID), has also been used to represent ‘the smallest difference in a score that is considered to be worthwhile or important.¹⁰ This method helps associate changes in disease measures with clinical relevance, as measured subjectively by patients and clinicians. Khanna et al. examined the MID in a clinical trial examining the efficacy of low-dose and high-dose D-penicillamine, and the MID estimate for the Rodnan skin score improvement ranged from 3.2 to 5.3.¹¹

THERAPIES FOR SKIN SCLEROSIS

Results evaluating therapies targeting cutaneous sclerosis of SSc are reviewed. These are categorized into immune-modulating treatments, antifibrotic agents, vasodilators and other investigational therapies.

IMMUNE-MODULATING THERAPIES (TABLE 35.1)

5-Fluorouracil:

In a 6-month randomized, double-blind, placebo-controlled study, intravenous 5-fluorouracil was evaluated in the treatment of scleroderma.¹² Skin assessment included a modified Rodnan skin score, and flexion and extension indices between the third finger and palmar crease. In the group receiving 5-fluorouracil, statistically significant improvement was observed in total skin score and extension index. Notably, toxicities were common in the treatment group.

TABLE 35-1—Therapies for Diffuse Cutaneous Systemic Sclerosist

Therapy	Outcome Measurement	Efficacy	Level of Evidence	Comment	Reference
Rituximab	MRSS	0	4	Improvement in dermal myofibroblast numbers	13
Rituximab	MRSS	0	4	Mean change in skin score was not significant	14
Mycophenolate mophetil with methyl prednisolone	MRSS	+	4	Skin score improved significantly after 1 year	21
Anti-thymocyte globulin and mycophenolate mophetil	MRSS	+	4	Significant decrease in skin score throughout 1 year study	22
PUVA phototherapy	Dermal thickness measured	+	2b	Dermal thickness significantly decreased	34
PUVA phototherapy vs. UVA1	Changes in collagen fibril diameter	0	4	Changes in collagen fibril diameter occurred deeper in the dermis after PUVA therapy as compared to UVA1 therapy	35
Cyclophosphamide	MRSS	+	1b	Significant difference between cyclophosphamide and placebo treatment arms	37
High-dose cyclophosphamide without stem cell rescue	MRSS	++	4	Significant improvement in skin score in treatment group	38
Cyclophosphamide vs. azathioprine	MRSS	+	2b	Significant improvement in cyclophosphamide group	36
Azathioprine as maintenance treatment following cyclophosphamide	MRSS	0	4	Modified Rodnan Skin Score did not deteriorate significantly	39
Cyclosporine	MRSS	+	4	Improvement in cutaneous abnormalities in severe scleroderma	40

Therapy	Outcome Measurement	Efficacy	Level of Evidence	Comment	Reference
Cyclosporine	MRSS	+	4	Skin thickness significantly decreased	41
Low-dose cyclosporine	Plicometry	+	4	Significant reduction in plicometry score	42
Halofuginone	MRSS	+	4	5/11 patients had 25% reduction in skin score	45
Thalidomide	MRSS	0	4	No benefit in measured skin score	46
Etanercept	MRSS	+	4	4/10 patients had improvement in skin score	48
Autologous stem cell transplantation	MRSS	++	4	63% of patients had significant improvement in Rodnan skin score	49
Autologous stem cell transplantation	MRSS	+	4	15/19 patients had improvement in skin score, and 35% patients relapsed within 10 months	50
Allogeneic stem cell transplantation	MRSS	++	4	Rodnan skin score decreased from 30 to 13	52
Allogeneic stem cell transplantation	Skin biopsy	+	4	One patient had resolution of dermal fibrosis on biopsy	53
Allogeneic stem cell transplantation	MRSS	++	4	Rodnan skin score decreased from 25 to 9	54
Colchicine	Skin elasticity	0	4	Improvement noted in skin elasticity	58
Imatinib	MRSS	+	4	Rodnan skin score decreased from 44 to 33	67
Imatinib	MRSS Skin tightening	+	4	Rodnan skin score reduction in both patients	68
Intravenous 5-fluorouracil	MRSS Extension index between 3 rd finger and palmar crease	+	1b	Significant improvement in total skin score and extension index	12
Chlorambucil	MRSS	0	1b	No significant difference from placebo	15
Intramuscular methotrexate	MRSS	+	1b	At 24 weeks, significantly more patients in methotrexate group had favorable response compared to placebo	17
Oral methotrexate	MRSS UCLA skin score	+	2b	Significant difference in Rodnan skin score change, but not in UCLA skin score	18
Oral methotrexate	Clinically judged improvement	0	2b	No significant improvement in skin parameters	16
Mycophenolate mofetil	MRSS	0	2b	No significant difference	20
D-penicillamine in low and high dose	MRSS	Not determined	1b	No significant difference between low and high dose	23
Extracorporeal photochemotherapy compared to D-penicillamine	Skin severity score Percent surface area involvement	+	1b	Significant improvement in skin severity score	27
Extracorporeal photochemotherapy	MRSS	0	1b	No significant difference between active and sham photopheresis	28

(Continued)

TABLE 35-1—Therapies for Diffuse Cutaneous Systemic Sclerosist (Continued)

Therapy	Outcome Measurement	Efficacy	Level of Evidence	Comment	Reference
Plasma exchange with D-penicillamine vs. D-penicillamine	MRSS	+	2b	Significant improvement of skin score in combination treatment group	30
Low-dose UVA1 phototherapy	MRSS	0	1b	No difference between treated and untreated hands	32
Low-dose UVA therapy	Clinical palpation and inspection	+	2b	No significant differences between UVA dosages of 5, 10, or 20 J/cm ²	33
Oral type 1 collagen	MRSS	0	1b	No significant difference in skin score change. Significant reduction in skin score in late-phase SSc patients only	25
Recombinant human tissue plasminogen activator	MRSS	+	1b	Significant difference between placebo and treatment	55
Aminobenzoate potassium	Skin mobility and thickening scores	0	1b	No significant difference	56
Urokinase	Ultrasound transverse and longitudinal scans	0	2b	Improvement in skin thickness; did not report statistical significance	57
Recombinant human relaxin	MRSS	+	1b	Significant difference between 25 µg/kg/day and placebo	60
Recombinant human relaxin	MRSS	0	1b	No significant difference between treatment groups and placebo	61
Interferon-α	MRSS Collagen synthesis from skin biopsy	0	1b	No significant difference	63
Interferon-γ	MRSS	0	2b	No significant improvement in skin score in treatment or control	62
Anti-TGF β (CAT-192)	Rodnan skin score	0	1b	No significant difference	64
Low and high dose iloprost	MRSS	0	2b	No significant change in skin score in both groups	69
Iloprost and cyclosporine-A vs. iloprost	Total plicometer skin score	+	2b	Significant improvement in iloprost and cyclosporine-A group	70
Dipyridamole and aspirin	Clinical skin induration	0	1b	No significant improvement	71
Ketanserin	Clinical skin evaluation	0	1b	No significant difference	72
Ketanserin	Clinical skin evaluation	0	1b	No significant difference	73
Stanozolol	MRSS	0	1b	No significant difference	74
Glyceryl trinitrate	Skin elasticity	0	2b	No significant difference	75
Intravenous pulse dexamethasone	MRSS	+	1b	Significant improvement in treatment group	76
Daily paraffin bath and hand exercise	MRSS Stiffness and skin elasticity - visual analog scale	+	2b	Elasticity and stiffness improved significantly; differences in skin score not reported	77
Minocycline	MRSS	0	4	No statistically significant difference between patients treated with minocycline and patients from D-penicillamine trial	81

Therapy	Outcome Measurement	Efficacy	Level of Evidence	Comment	Reference
PVAC	MRSS	+	1b	Significant improvement in the 15 µg PVAC arm but worsening of skin score in 50 µg PVAC arm	78
Factor XIII	Clinical assessment	+	1b	Significant difference between placebo and treatment	79

MRSS, modified Rodnan skin score; PUVA, psoralen + ultraviolet A; UVA, ultraviolet A; PVAC, psoriasis vaccine.

with 96% of patients having gastrointestinal complaints, which generally responded to dose reduction.

Rituximab

The safety and efficacy of rituximab, an anti-CD20 monoclonal antibody that depletes mature B-lymphocytes, has been examined in scleroderma patients. There have been two open label trials with conflicting results. In the first, eight patients received an infusion of 1000 mg rituximab at baseline and again at day 15, along with 100 mg methyprednisolone. Both modified skin score and histopathologic evaluation of the skin were examined. Rituximab induced effective B cell depletion in all patients and there was a significant change in skin score by week 24 ($p<0.001$). Furthermore, there was improvement measured in dermal myofibroblast numbers and the dermal hyalinized collagen content.¹³ Overall, treatment with rituximab was well tolerated. In another open-label study examining the safety and efficacy of rituximab, 15 patients with diffuse cutaneous systemic sclerosis received two intravenous doses of rituximab 2 weeks apart.¹⁴ The primary outcome measure was modified Rodnan skin thickness score after 6 months compared to baseline. The mean change in skin score was not significant. Rituximab treatment did result in depletion of circulating B cells and depletion of dermal B cells, with little effect on SSc-associated autoantibodies. Treatment with rituximab did not have a significant beneficial effect on skin disease, although it appeared safe and well tolerated.

Chlorambucil

Chlorambucil was compared to placebo in a 3-year randomized double-blind study (n=65).¹⁵ Chlorambucil is an immunosuppressive agent and the treatment group developed significantly more decrease in white blood cell count, platelet count, and lymphocyte counts as compared to placebo. Semiquantitative skin scores showed no significant difference between treatment groups. Overall, 3 years of treatment did not show any significant benefit for patients with SSc.

Methotrexate

In a trial of 18 patients with systemic sclerosis, methotrexate versus placebo was tested for 18 months.¹⁶ Clinical improvement was observed but no statistically significant

improvement in skin parameters were seen in the treatment group. Anorexia, nausea, and vomiting were common side effects and nine patients (3 in the methotrexate group) total dropped out of the study due to noncompliance or toxicity.

In a randomized, double-blinded trial, methotrexate was compared to placebo using a 24-week treatment period followed by 24-week observation period.¹⁷ Scleroderma patients received weekly injections of 15 mg methotrexate (n=17) or placebo (n=12). Rodnan total skin score was assessed. By week 24, Rodnan skin score changes were -0.7 and 1.2 in the methotrexate and placebo groups, respectively ($P<0.06$). Six patients had methotrexate temporarily held because of elevated liver function tests and two patients in the methotrexate group withdrew from the study because of scleroderma renal crisis and persistent headaches.

In a multicenter trial (n=71) patients were treated with either methotrexate or placebo for 12 months.¹⁸ The primary outcomes measured were modified Rodnan skin score and the UCLA skin score. Methotrexate was begun at 10 mg/week and gradually titrated to 15 mg/week. When between-group differences for changes in score were studied using intent to treat analysis, methotrexate had a favorable effect on skin scores (-4.3 vs. 1.8 in placebo group, $p<0.009$). However, the differences in the UCLA skin score were not statistically significant, and the groups were mismatched at baseline in a manner that might favor methotrexate. The authors concluded that the between-group differences were small and there was not enough evidence to show that methotrexate is significantly effective for diffuse SSc. Interestingly, this trial was recently re-examined, and the results were reanalyzed using a Bayesian analysis.¹⁹ Three outcomes were studied including the modified Rodnan skin score, ULCA skin score, and physician global assessment of disease activity. The probability of beneficial treatment effect was computed. The probability that methotrexate treatment results in better mean outcomes than placebo was 94% for modified skin score, 96% for UCLA skin score and 88% for physician global assessment. The authors concluded that a Bayesian analysis for uncommon disease trials could allow for more clinically relevant conclusions.

Mycophenolate Mofetil

Mycophenolate mofetil (MMF) was studied in a retrospective trial of 172 patients.²⁰ MMF is an inosine

monophosphate dehydrogenase inhibitor which inhibits de novo guanosine nucleotide synthesis. It helps suppress proliferation of both T and B-lymphocytes. Data covering a 5-year period from the beginning of treatment was collected. While treatment with MMF was overall well tolerated, there was no significant difference between the treatment and control groups using modified Rodnan skin score.

Additionally, a pilot study was conducted evaluating the efficacy and safety of a treatment strategy combining mycophenolate mofetil, intravenous methylprednisolone and low-dose glucocorticoids.²¹ Nine patients were recruited based on their severe skin involvement (modified Rodnan skin score of at least 15) and received 3 consecutive daily methylprednisolone pulse treatments followed by 5 additional monthly methylprednisolone pulse treatments. Mycophenolate mofetil dosed at 0.5 g twice daily for 1 week then 1g twice daily and oral prednisolone at 5-10 mg/day were also administered for 1 year. Modified Rodnan skin score significantly improved at 1 year. Patients tolerated the triple combination regimen well and no patients suffered from renal impairment.

Another pilot study assessed the efficacy and safety of anti-thymocyte globulin followed by mycophenolate mofetil in the treatment of recent-onset diffuse scleroderma.²² Thirteen patients with recent-onset scleroderma were treated with antithymocyte globulin first for 5 days followed by mycophenolate mofetil for 1 year. Modified skin score was measured and decreased throughout the study from 28 at baseline to 17 following the 12-month treatment period ($p<0.01$). Interestingly, hand contractures worsened throughout the study. Overall, therapy with mycophenolate mofetil was well tolerated but five patients developed serum sickness after treatment with antithymocyte globulin.

D-penicillamine

D-penicillamine was proposed as a possible therapy for SSc because it interferes with molecular cross-linking of collagen and has immunomodulatory effects. In a double-blind, randomized study of 134 patients, high-dose D-penicillamine was compared to low-dose D-penicillamine in the treatment of cutaneous SSc.²³ Altogether, 68 patients with early diffuse cutaneous SSc completed 2 years of treatment. Using the modified Rodnan skin thickness score, there was no significant difference in skin score change between the two treatment groups. The skin score dropped by 4.8 ± 10.3 units in the high-dose group and 6.9 ± 8.4 units in the low-dose group. There were 20 withdrawals related to adverse events, 80% of which occurred in the high-dose group. Notably, in this trial, toxicity was increased in the high-dose group, therefore demonstrating a biologic response. However, this study demonstrated no differences in efficacy between a D-penicillamine dose of 125 mg every other day and a mean dose of 822 mg daily. The Authors concluded that

if D-penicillamine was to be used to treat SSc, there is no advantage to using dosages higher than 125 mg every other day. This argued in favor of using placebo controls in studies until an active control is found which is truly a disease-modifying agent. The authors explained that without using a placebo control, the efficacy of D-penicillamine remains unclear.

Bovine Type I Collagen

In patients with diffuse cutaneous SSc, the safety and efficacy of oral bovine type I collagen was examined (n=168).²⁵ Oral type I collagen at 500 µg/day or placebo was administered for 12 months. Authors sought to induce oral immune tolerance to type I collagen and assess its ability to improve skin thickness. The modified Rodnan skin score was assessed, and both intent-to-treat and modified intent-to-treat analyses showed no significant difference in the mean change of skin score between the two groups. However, patients with late-phase (disease greater than 3 years) diffuse cutaneous SSc experienced a significant reduction in skin score compared to placebo-treated patients when analyzed at 15 month follow-up ($p=0.0063$). This result was only significant, however, using an "as treated" analysis, while an intent-to-treat analysis revealed a nonsignificant improvement. The authors concluded that type I collagen treatment may provide benefit for patients with late-phase diffuse cutaneous SSc.

Photopheresis/Plasma Exchange

Photopheresis is a therapy combining ultraviolet A (UVA) irradiation with 8-methoxysoralen.²⁶ There is repeated extracorporeal exposure of peripheral blood lymphocytes to UVA light and lymphocytes are subsequently reinfused into the patient. In a multicenter, randomized, investigator-blinded clinical trial (n=79) extracorporeal photochemotherapy treatment administered monthly was compared with D-penicillamine in the treatment of SSc; patients had progressive skin involvement for the previous 6 months.²⁷ Blinded examiners evaluated skin severity score, percent surface area involvement and performed skin biopsies. Following 6 months of treatment, 68% of patients receiving photochemotherapy achieved significant improvement in skin severity score as compared to baseline skin score; as noted earlier, small, but clinically meaningful changes in skin score are not always statistically significant. For patients treated with D-penicillamine, no cutaneous disease measures improved significantly at 6 months, the difference in response rate between the groups was significant ($p=0.02$). Skin biopsies illustrated a correlation between clinical improvement and decreased dermal thickness. No patients required discontinuation of extracorporeal photochemotherapy.

Extracorporeal photochemotherapy was investigated in a randomized, double-blind placebo-controlled trial

(n=64).²⁸ These patients all had clinical scleroderma of less than 2 years duration which is thought to represent the group with the most aggressive clinical disease behavior.²⁹ Patients received either active or sham photopheresis monthly for 12 months. After 6 and 12 months, statistically significant improvement in modified Rodnan skin score was found in those who received active treatment ($p=0.0024$ and $p=0.008$ respectively). Between active and sham photopheresis groups, there was insufficient statistical power to reveal a difference in skin scores; a power analysis revealed that 60 patients per treatment arm would have been needed for a p-value of 0.05 or less. However, the authors noted a trend to a difference that did not reach significance ($p=.119$ at 6 months and $p=.129$ at 12 months).

Plasma exchange combined with D-penicillamine treatment was compared to D-penicillamine alone in the treatment of 29 patients with SSc.³⁰ Total skin score was measured. Following six plasma exchange treatments, total skin score showed significant improvement in the group receiving both plasma exchange and D-penicillamine. The most common side effect was hypotension, which resolved following transfusion.

Ultraviolet A1 Phototherapy

UVA1 irradiation induces apoptosis of T-cells, which infiltrates the skin and can reduce collagen deposition in the dermis.³¹ Ultraviolet A1 treatment (UVA1) ranging from 340-400 nm was tested in an investigator-blinded, controlled trial of 9 patients with acrosclerosis.³² A modified Rodnan skin thickness score was used and cutaneous thickness assessed on each hand after clinical palpation of both palmar and dorsal sides. Low-dose UVA1 treatment was used 3 times weekly for 14 weeks. While the mean skin score improved, the improvement was not different between treated and untreated hands.

UVA Phototherapy

Low-dose UVA phototherapy was examined in a trial of 15 patients with SSc.³³ Patients were allocated randomly into three treatment arms receiving 5, 10, or 20 J/cm². Patients were judged clinically by inspection and palpation (non-blinded). There was clinical improvement in all groups after 20 sessions, but no comparable differences were noted between the different UVA dosages. The authors concluded that lower doses of UVA are just as effective as the higher dose of UVA (20 J/cm²) for the treatment of cutaneous SSc.

PUVA Phototherapy

PUVA treatment (photochemotherapy) refers to combining UVA light, at a wavelength of 320-400 nm, with the use of 5- or 8-methoxysoralen, which helps sensitize cells to light. Psoralens are thought to intercalate between DNA,

and form crosslinks, which can prevent replication of DNA following exposure to UVA light. Photochemotherapy was studied with quantitative echography in patients with SSc.³⁴ The dermal echo intensity and dermal thickness were measured before and after treatment. Thirteen patients with SSc were studied, randomly receiving either oral photochemotherapy with 20 mg methoxysoralen or topical 0.3% methoxysoralen. UVA irradiation was started at $\frac{1}{2}$ minimal phototoxic dose. Overall, the dermal echo intensity significantly increased compared to baseline while dermal thickness significantly decreased. Authors concluded that photochemotherapy was more likely to improve dermal edema, not fibrosis.

In a recent study of three patients with diffuse SSc, two patients were treated with PUVA and one treated with UVA1 irradiation.³⁵ UVA1 therapy began with a single dose of 10 J/cm² and the exposure dose was gradually increased to 60 J/cm². For PUVA therapy, topical 0.3% 8-methoxysoralen was applied to the patient's skin and a single dose of 0.6 J/cm² was used first, and the exposure dose was gradually increased to 2.4 J/cm². The total cumulative dose in the two patients was 65 J/cm² and 164 J/cm². Skin specimens were taken from the forearms of patients before and after treatment. In the patient treated with UVA1 therapy, alteration of collagen fibrils was seen in the upper reticular layer and the number of large collagen fibrils decreased. The patients treated with PUVA therapy demonstrated similar changes in the upper reticular to the middle reticular layer. The median collagen fibril diameter decreased by 10 nm. Furthermore, spaces between collagen fibrils widened in all patients. Overall, changes in collagen fibril diameter occurred deeper in the dermis after PUVA therapy as compared to UVA1 therapy.

Cyclophosphamide

Cyclophosphamide, a cytotoxic immunosuppressive medication which modulates lymphocyte function, and the immunosuppressant azathioprine were compared in a randomized unblinded trial for 18 months (n=60).³⁶ Patients also initially received a course of prednisolone during the first 6 months of the trial. This trial evaluated patients for 18 months with 30 patients receiving oral cyclophosphamide at 2 mg/kg daily for 12 months followed by a maintenance dose of 1 mg/kg daily, and a comparison group of 30 patients receiving azathioprine at 2.5 mg/kg daily for 12 months followed by 2 mg/kg daily. Following treatment there was a statistically significant improvement in the modified Rodnan skin score in the cyclophosphamide group ($p<0.01$), but not in the azathioprine group (no trend towards improvement or worsening). The difference between the two groups in modified Rodnan skin score was statistically different ($p<0.001$). Despite its limitation as an unblinded trial, authors concluded that cyclophosphamide might be a potential disease-modifying agent for cutaneous SSc.

In a multicenter, randomized, placebo-controlled trial, the effect of oral cyclophosphamide was evaluated in 158 patients with scleroderma.³⁷ Patients received oral cyclophosphamide at <2 mg/kg body weight/day or placebo for 1 year and were followed for a subsequent year. In the 85 patients who had diffuse cutaneous sclerosis, modified Rodnan skin score at 1 year showed a significant difference between the two groups and favoring the cyclophosphamide treatment arm (-3.06 , $p=0.008$), although this is on the borderline of clinical significance.

High-dose cyclophosphamide without stem cell rescue was investigated in an open-label uncontrolled study for patients with diffuse cutaneous scleroderma.³⁸ Patients were treated with intravenous cyclophosphamide (at 50 mg/kg) for four consecutive days followed by granulocyte colony-stimulating factor (5 µg/kg/day). The primary endpoint was modified Rodnan skin score. The percentage reduction in Rodnan skin score in 5 evaluable patients 1 month following treatment was 60%, 55%, 41%, 31%, and 0%. Three patients demonstrated sustained improvement for 12, 12, and 24 months, while the other two patients relapsed. There was one patient death as a result of infection after neutrophil count recovery. The authors concluded that the use of high-dose cyclophosphamide could lead to a significant improvement in skin score.

Azathioprine

Azathioprine has also been investigated in the treatment of systemic sclerosis. After 1 year of treatment with low-dose pulse cyclophosphamide in patients with early diffuse systemic sclerosis, 13 patients underwent treatment with azathioprine 100 mg/day in a prospective 1-year study.³⁹ Overall, authors concluded that the improvement from a year of cyclophosphamide therapy was maintained with azathioprine treatment. The modified Rodnan skin score did not deteriorate significantly and azathioprine may have a role in maintaining improvement, which is induced by low-dose pulse cyclophosphamide although controlled studies have not been pursued.

Cyclosporine

Cyclosporine is an immunosuppressant agent, which was first used in organ transplant recipients. Cyclosporine binds to cyclophilin, leading to calcineurin inhibition and a blockade subsequently resulting in decreased levels of inflammatory cytokines such as interleukin-2. In an open-label pilot study, the efficacy of cyclosporine was investigated in eight patients with severe scleroderma.⁴⁰ Cyclosporine was initiated at 5 mg/kg/day and then adjusted to a mean dosage of 4.3 mg/kg/day. Following 6 to 12 months of treatment, cutaneous abnormalities improved in seven patients and no serious side effects were observed. No information described exact magnitude of skin score change, but authors concluded that cyclosporine is mainly

effective in skin involvement of scleroderma and possibly in other organ manifestations as well.

In an open-label study evaluating the safety and efficacy of cyclosporine for 48 weeks, ten patients were treated with cyclosporine and the skin score at entry and after treatment were compared.⁴¹ Skin thickening was significantly decreased ($p<0.001$) in the treatment group and adverse reactions were usually transient and associated with a cyclosporine dose of at least 3-4 mg/kg/day.

In a long-term study of low-dose cyclosporine, 9 patients who received cyclosporin treatment for diffuse systemic sclerosis with treatment periods ranging between 3-5 years at a mean dosage of 2.5 mg/kg/day were examined.⁴² Plicometry was used as a measurement of skin disease, and statistically significant reduction in the mean score was noted at 2 and 3 years after treatment with cyclosporine was initiated. Overall, low-dose long-term treatment with cyclosporine was well tolerated and no renal impairment or increases in blood pressure were observed throughout the 3 years.

In a routine immunology clinic, 16 patients who had been given cyclosporine (13 of which had been treated specifically for skin tightness) were identified.⁴³ Half of the patients noticed significant skin softening during cyclosporine treatment. However, side effects, particularly hypertension, were common and contributed to withdrawal in 12 of the 13 patients identified.

Halofuginone

Halofuginone acts by blocking the activated of Smad3 protein, interfering with the synthesis of TGF-β and potentially reducing collagen synthesis by fibroblasts.⁴⁴ Topical 0.1% halofuginone ointment appears to be safe and well tolerated. A treatment regimen for 6-months resulted in significant reduction of collagen type I in affected skin of patients with cutaneous sclerosis.⁴⁵

In a phase II trial designed to assess the safety and efficacy of halofuginone for diffuse SSc, the modified Rodnan skin thickness score was used as primary endpoint. Thirteen patients were treated once daily with topical 0.01% halofuginone (randomly assigned to either the right or left upper extremities) and 11 patients completed a 6-month treatment course. The most frequently reported adverse event was dermatitis of varying degree that did not result in cessation of treatment. Five patients met responder criteria of a 25% reduction in total skin score on the treated arm and the average time for response was 2.6 months. Halofuginone is being further investigated for the treatment of dermal fibrosis.

Thalidomide

Thalidomide was investigated in a prospective, nonrandomized open-label study in 11 patients with systemic

sclerosis.⁴⁶ Initially, thalidomide was administered at 50 mg/day up to a final dose of 400 mg/day. This led to complete healing of digital ulcers, but there was no benefit reported in modified skin score after 12 weeks of treatment. Furthermore, there was some development of extremity edema and dry skin in the patients receiving thalidomide. However, histologic comparison of skin biopsies did show changes in skin fibrosis in patients treated with thalidomide, and plasma levels of IL-12 and TNF- α were also increased in treated patients.

Etanercept

Etanercept is an inhibitor of tumor necrosis factor- α , (TNF- α) which is a proinflammatory cytokine produced by T-cells, which stimulated the synthesis of many other inflammatory cytokines such as IL-1, IL-6 and IL-8. Etanercept is a fusion protein of a soluble TNF receptor joined to human immunoglobulin.⁴⁷ In a pilot open-label study, 10 patients with early diffuse SSc were treated with etanercept at a dose of 25 mg subcutaneously twice weekly.⁴⁸ Following 6 months of therapy, four patients experienced an improvement in skin score, six patients experienced no improvement, and all patients tolerated the injections well.

High-Dose Immunosuppressive Therapy Followed By Autologous Stem Cell Transplantation

Two groups, one in the U.S. and one in Europe, have reported on their experience with the largest cohort of patients to be treated with this modality. An open-label multicenter trial of 34 patients with diffuse cutaneous SSc in the U.S. evaluated the efficacy of high-dose immunosuppressive therapy and autologous CD34-selected hematopoietic cell transplantation.⁴⁹ The immunosuppressive treatment included total body irradiation, cyclophosphamide at 120 mg/kg and anti-thymocyte globulin. Of the 27 evaluable patients, 63% had sustained response at a median follow-up of 4 years with a major improvement in modified Rodnan skin score (a decrease by 22 points, $p<0.001$). This equates to skin improvement of approximately 70%. Biopsies also confirmed a statistically significant decrease of dermal fibrosis as compared to baseline ($p<0.001$). During the study, there were 12 deaths of which eight were related to transplantation and four related to scleroderma progression. The estimated 5-year progression-free survival was 64%. Overall mortality at 5 years was 36% and the treatment-related mortality was 23%; relapse rate was not discussed.

Another group reported the results of a multicenter study in Europe using autologous hematopoietic stem cell transplantation in 57 patients.⁵⁰ Differing conditioning regimens, which included cyclophosphamide, were used,

and, unlike the U.S. study, most of the patients did not undergo total body irradiation. Hematopoietic stem cells were CD34-selected or further T cell-depleted. Fifteen out of 19 patients had an improvement in Rodnan skin score by at least 25% at 2 years. Overall, 35% of patients with initial partial response ($n=13/32$) or a complete response ($n=3/14$) relapsed within 10 months after stem cell transplant. Five patients died from treatment-related complications and eight from disease progression. Authors of this report concluded that the response seen in two-thirds of patients overall following transplantation was durable with an acceptable transplant-related mortality. Based on these data, there are currently two prospective randomized phase III studies to evaluate autologous stem cell transplantation in North America and Europe.⁵¹

High-Dose Immunosuppressive Therapy Followed By Allogeneic Stem Cell Transplantation

Compared to the autologous setting, there is scant experience using allogeneic stem cell transplantation for SSc. This methodology is proposed by some in response to the high relapse rate seen using the autologous transplantation, and it is proposed that a “graft versus autoimmunity” response might be a major benefit of the allogeneic transplant protocol, resulting in a lower relapse rate. At this time, there are only case reports of success in a handful of patients. A 40-year old patient with diffuse scleroderma and interstitial pneumonia was treated with an allogeneic peripheral blood stem cell transplantation from an HLA-identical sibling following conditioning with total-body irradiation and fludarabine.⁵² Cyclosporine and mycophenolate mofetil were also used as prophylaxis for graft-versus-host disease (GVHD); the patient tolerated transplantation well with no infection or GVHD. One year following transplantation, the patient’s skin score had decreased dramatically from 30 to 13. The patient did develop membranous glomerulopathy caused by chronic GVHD treated successfully with prednisolone.

Nash et al. evaluated the safety and efficacy of allogeneic hematopoietic stem cell transplantation after myeloablative conditioning in two patients.⁵³ The conditioning regimen included treatment with cyclophosphamide, antithymocyte globulin, and busulfan. Cyclosporine and methotrexate were used for GVHD prophylaxis. Bone marrow was transplanted from siblings who were HLA-identical. For the first patient, 5 years after stem cell transplant the patient had near complete resolution of scleroderma with resolution of dermal fibrosis from serial skin biopsies. The patient had no complications of GVHD. Patient two had skin toxicity from the initial conditioning regimen, and the patient experienced an improvement in scleroderma, but died from a fatal opportunistic infection 17 months following stem cell transplant.

Loh et al. reported a patient with diffuse cutaneous SSc who successfully underwent allogeneic hematopoietic stem cell treatment from an HLA-identical sibling.⁵⁴ The patient's baseline Rodnan skin score was 25. The conditioning regimen consisted of 200 mg/kg of cyclophosphamide and alemtuzumab; cyclosporine and mycophenolate were used for prophylaxis of GVHD. Rodnan skin score decreased to nine at 26 months following transplantation, and the patient tolerated treatment well with no development of GVHD.

ANTIFIBROTIC AGENTS (TABLE 35.1)

Fibrosis is an important component of the progression of skin disease in scleroderma, consisting of deposition of newly synthesized connective tissue such as collagens. Antifibrotic therapies are aimed to reduce the synthesis and polymerization of collagen, or to enhance collagenase activity.

Recombinant Human Tissue Plasminogen Activator

Low-dose (10 mg) recombinant human tissue plasminogen activator was one of the first antifibrotic agents examined in a double-blinded, placebo-controlled crossover trial (n=14).⁵⁵ The mean change of Rodnan skin score in the placebo arm was an increase of 0.8, while the mean change in the treatment group was decrease by 5.4. A significant difference was observed in the mean change of the Rodnan skin score between placebo and treatment arms ($p<0.001$) and 10 patients showed mild to moderate improvement in Rodnan skin score.

Aminobenzoate Potassium

In a 48-week prospective, double-blind randomized study the efficacy of the antifibrotic agent aminobenzoate potassium was compared to placebo for the treatment of skin manifestations of scleroderma.⁵⁶ Skin mobility and thickening scores were assessed. Of 146 patients in the study, only 52% completed the study. No clinical or statistically significant differences were seen between the placebo and treatment groups for the skin mobility and thickening score changes.

Urokinase

Urokinase is produced by endothelial cells and seems to play a role in endothelial cell migration and revascularization but its exact mechanism of action in this study is not clear. A 4-month placebo-controlled randomized trial of urokinase therapy in 36 patients was conducted with measurements of ultrasonography of the skin.⁵⁷

Ultrasound was used as a noninvasive technique to study the skin and subcutis with both transverse and longitudinal scans (nonblinded assessment). Ultrasound measurement showed diminished echogenicity of the epidermis and dermis and a noticeable improvement in skin thickness.

Colchicine

In addition to its anti-inflammatory activity, colchicine has the ability to interfere with synthesis of collagen by depolymerizing microtubules and reducing fibroblast proliferation. One uncontrolled study evaluated colchicine in 19 patients with scleroderma with a follow-up period ranging from 19 to 57 months.⁵⁸ The average dosage used was 0.6 mg twice daily, and there was improvement noted in skin elasticity; skin score was not measured. Overall, colchicine was well tolerated and the most common adverse event was diarrhea.

Relaxin

Relaxin is a protein primarily secreted by the ovary and placenta, which has tissue remodeling activity. Recombinant human relaxin is thought to reduce synthesis of dermal fibroblast collagen as well as to degrade existing collagen.⁵⁹ To assess the safety and efficacy of recombinant human relaxin in a double-blind placebo-controlled trial, 68 patients were randomized to receive treatment with 25 or 100 µg/kg of human relaxin versus placebo for 24 weeks.⁶⁰ Modified Rodnan skin score was measured. Patients receiving 25 µg/kg/day relaxin had reduction in mean skin score from 27.5 at screening to 18.8 after 24 weeks; patients receiving 100 µg/kg/day of relaxin had reduction in mean skin score from 26.3 at screening to 24.1 after 24 weeks. Patients receiving 25 µg/kg/day of human relaxin had significantly lower skin scores compared to those receiving placebo, but patients receiving 100 µg/kg/day did not show any difference from placebo. The authors suggested that possibly a higher dose of relaxin fails to stimulate collagenase secretion. Adverse events included anemia, site irritation, local infection, and pain at the injection site.

Recently human relaxin was evaluated in a larger, double-blind, placebo-controlled trial (n=195).⁶¹ Placebo was compared with 10 µg/kg/day and 25 µg/kg/day for 24 weeks in patients with stable, moderate-to-severe diffuse SSc. In both treatment groups, the modified Rodnan skin score did not decrease significantly as compared to placebo. Relaxin was associated with serious renal adverse events and hypertension, although most of these events occurred after abruptly stopping infusion. We conducted a meta-analysis of these two randomized trials, which indicates that relaxin is more effective than placebo in reducing the MRSS by 0.668 (0.393, 0.944) using a fixed effects model. However, this small a change in MRSS is not of clinical significance.

Interferon- α

Interferon- α (IFN- α) has been shown to inhibit collagen synthesis and fibroblast proliferation *in vitro*.⁶² The efficacy of this agent was examined in the treatment of diffuse cutaneous SSc for patients with early skin involvement, in a randomized double-blind placebo-controlled study.⁶³ Thirty-five patients received injections of either IFN- α or placebo for 12 months. There was a greater improvement in Rodnan skin score in the placebo group after 12 months. Skin biopsies did not demonstrate a significant decrease in collagen synthesis in the treatment groups. The authors concluded that this agent does not effectively treat cutaneous manifestations of SSc and may be potentially deleterious.

Interferon- γ

Interferon-gamma (IFN- γ) treatment for systemic sclerosis was investigated in a randomized-controlled trial in 44 patients with mean duration of skin sclerosis for 10.8 years.⁶⁴ Patients received recombinant IFN- γ treatment 3 times weekly for 12 months. Skin involvement was measured with a modified Rodnan skin score of 15 sites. While the skin scores tended to improve in the treatment groups, they did not improve significantly in the overall analysis of the treatment or control group. There was a high frequency of mild and moderate influenza-like adverse events in the treatment group.

Recombinant Human Antibody CAT-192

A recombinant human antibody (CAT-192) which neutralizes transforming growth factor β 1 (TGF β 1) was evaluated in the treatment of diffuse cutaneous SSc.⁶⁵ Forty-five patients were assigned to receive placebo or three different dosages of CAT-192. The Rodnan skin thickness score was assessed. The Rodnan skin score improved in all groups but there was no significant evidence for a treatment effect of CAT-192. Additionally, there were more adverse events, including serious adverse events, in patients treated with CAT-192. Authors concluded that CAT-192 did not show efficacy in doses up to 10 mg/kg. Authors also noted that effective prevention of fibrosis, based on animal models, requires that multiple isoforms of TGF β be blocked (not just one isoform), which may potentially explain why CAT-192 did not show evidence of efficacy in the trial.

Imatinib

Imatinib mesylate is a tyrosine kinase inhibitor which interferes with the signaling of TGF- β as well as other kinases that might be involved in the fibrotic response, blocking extracellular matrix synthesis both *in vitro* and in

mouse models.⁶⁶ Imatinib mesylate was used in a 24-year-old patient with diffuse systemic sclerosis of 7 years duration which was severe and progressive.⁶⁷ Within 6 weeks after initiating imatinib treatment at 400 mg/day orally, the patient's skin score decreased from 44 to 33 along with improvement in flexion contractures. Furthermore, at 3 and 6 months the patient's modified skin score was further reduced to 28. Overall, the treatment was well tolerated and no adverse effects were noted.

In another report, two patients with early diffuse cutaneous SSc experienced a reduction in skin sclerosis following therapy with imatinib mesylate.⁶⁸ One patient was treated with 3 months of oral imatinib 100 mg daily and the other with 6 months of oral imatinib at 200 mg daily. Both patients experienced improvement in skin tightening and the modified Rodnan skin score improved in patients 1 and 2 from 36 to 21 and 20 respectively. Immunohistochemical analyses of skin biopsy specimens showed a reduction in phosphorylated platelet-derived growth factor receptor and Abl (both tyrosine kinases thought to play a role in fibrosis) with imatinib therapy. Furthermore, an imatinib-responsive signature specific for diffuse cutaneous SSc was identified ($p<10^{-8}$).

VASODILATORS

Iloprost

Recently, differing dosages of iloprost were compared for the treatment of skin thickening in SSc.⁶⁹ Iloprost is a synthetic analogue of prostacyclin PGI₂ that dilates both systemic and pulmonary arterial vascular beds. Patients were randomized to either high or low-dose intravenous iloprost treatment for 21 days. There was no significant difference between low-dose and high-dose iloprost in reduction of skin score. One year following therapy, the modified Rodnan skin score was unchanged in both groups.

Cyclosporine A and iloprost were compared to iloprost alone in a study of 20 patients for 12 months.⁷⁰ A significant improvement in skin score was noted ($p=0.008$) only in the group receiving both low-dose cyclosporine A and iloprost. In this trial, scores were assessed using plicometry by measuring the plica of each skin area. Additionally, there was a significant reduction of interleukin-6 serum concentration in this group, suggesting that interleukin-6 may play a role in the skin improvement noted.

OTHER THERAPIES

Dipyridamole

In a randomized, double-blind controlled study of patients with early scleroderma (n=28) patients received dipyridamole and aspirin versus placebo for 1-2 years.⁷¹ Clinical

skin induration scores showed no significant improvement in either treatment or placebo groups.

Ketanserin

In a randomized double-blind study (n=24), ketanserin, a specific S2-serotonergic receptor antagonist, was compared to placebo in a 6-month trial.⁷² Ketanserin failed to produce an improvement in clinical signs and symptoms compared to placebo, including modified Rodnan skin score. In another randomized study (n=27) patients were treated with ketanserin for 6 months.⁷³ No significant difference was observed between the two groups with regard to skin changes and more patients in the ketanserin group experienced dysphagia.

Stanozolol

Stanozolol is an anabolic steroid with low virilizing potential, which can enhance impaired fibrinolytic activity. This was tested in a double-blind, randomized placebo-controlled trial of 24 patients.⁷⁴ Measurement of skin disease with modified Rodnan skin score showed reduction in the treatment group, but was not significant ($p=0.37$). Rodnan skin score was unchanged in the placebo group. Magnitude of differences in Rodnan skin score not stated.

Glyceryl Trinitrate

Glyceryl trinitrate was used in a trial of 10 patients with sclerodermatosus skin change in a placebo-controlled trial for 4 weeks.⁷⁵ The topical medication was applied to the forearm only and skin elasticity was measured with the Cutech Extensometer. The application of topical glyceryl trinitrate had no effect on skin elasticity.

Dexamethasone

In a randomized double-blind study (n=35) patients received intravenous dexamethasone pulse therapy or placebo, with pulse therapy repeated once monthly for 6 months.⁷⁶ Rodnan skin score demonstrated significant improvement in the treatment group, decreasing from $28.5 +/ - 12.2$ to $25.8 +/ - 12.8$. In the placebo group, total skin score increased from $30.6 +/ - 13.2$ to $34.7 +/ - 10$. Authors concluded that intravenous pulse dexamethasone may be useful in the treatment of diffuse systemic sclerosis; difference between the two groups not stated. Adverse effects were limited to increase in upper respiratory infections.

Paraffin Bath

In 17 patients with SSc, one hand was treated with daily paraffin bath and hand exercise while the other was treated

only with exercise, functioning as a control.⁷⁷ Pain, stiffness, and skin elasticity were assessed by self-rating using a visual analogue scale. Skin thickness was determined by palpation using the modified Rodnan skin score (nonblinded). Assessments were made at three sites using the index finger, dorsum of hand and the forearm with a maximum score of 9 points. Perceived stiffness and skin elasticity improved significantly in the hand treated with paraffin baths for 6 months. Differences in skin thickness were not analyzed.

PVAC

PVAC (psoriasis vaccine) derived from deglycolipidated *Mycobacterium vaccae* was evaluated in a double-blind, randomized placebo-controlled trial using intradermal injections in patients with diffuse SSc for 24 weeks.⁷⁸ The primary efficacy endpoint was change in modified Rodnan skin score, which improved by 20.6% in the 15 µg PVAC arm but worsened by 16.7% in the 50 µg PVAC arm. Use of PVAC injections was well tolerated with no serious adverse events.

Factor XIII

The efficacy and tolerability of Factor XIII treatment was compared to placebo in a double-blind randomized cross-over trial of 25 scleroderma patients.⁷⁹ Patients received intravenous Factor XIII or placebo for 3 weeks. Clinical assessments made by physicians and patients indicated that treatment with Factor XIII improved cutaneous SSc significantly better compared to placebo (specific endpoint was vague) and this was supported by significant improvement in a function index used to assess the degree of motor disability.

Minocycline

Eleven patients with early scleroderma were treated with minocycline at 100 mg daily for 4 weeks followed by 200 mg daily for 11 months. Four of the patients experienced complete resolution of skin involvement.⁸⁰ A larger study evaluated minocycline in an open-label multicenter trial (n=31) to determine if minocycline therapy improved skin thickness by at least 30% (which was considered a level of improvement unlikely to occur because of the natural history of the disease).⁸¹ Patients with early diffuse SSc of at least 5 years duration were treated with oral minocycline for 1 year, and the primary measured endpoint was modified Rodnan skin score. Thirty-one patients were included for analysis and there was no statistically significant difference in skin score change between minocycline treated patients and subjects reported from the D-penicillamine trial, used as comparitors. Comparison of the modified skin score in the minocycline-treated patients and previously reported D-penicillamine trial, when adjusted for disease duration,

showed no difference and no treatment effect. The authors concluded that the change seen in the modified Rodnan skin score was similar to what may be expected because of the natural disease course and minocycline is not an effective therapy for SSc.

THERAPIES FOR DIGITAL ISCHEMIC ULCERS (TABLE 35.2)

Digital ulcers, a prominent vascular complication occurring in up to half of patients with limited or diffuse SSc, are extremely painful cutaneous lesions, which can lead to significant disability.⁸² The pathogenesis of these ulcers is multifactorial, and progressive tissue ischemia and endothelial cell injury are thought to play a critical role.⁸³ Furthermore, there may be increased production of vasoconstrictors, decreased production of vasodilating compounds such as nitric oxide, intraluminal thrombosis and vasospasm secondary to Raynaud's phenomenon which lead to decreased tissue oxygenation in the pathogenesis of digital ulcers.⁸⁴

In a randomized, double-blind trial of 84 patients, 2% dimethyl sulfoxide (DMSO), 70% DMSO and normal saline were compared for the topical treatment of digital ulcers associated with SSc.⁸⁵ Among all three groups, no significant differences were found in the number of open ulcers, surface area of ulcers, infection rates of ulcers or patient pain assessments. Improvement in any patient

could not be attributed to a specific therapy and more than 25% of patients in the 70% DMSO group withdrew because of significant skin reactions.

Quinapril was evaluated in a double-blind, placebo-controlled study of 210 patients with either limited systemic sclerosis or with Raynaud phenomenon and the presence of SSc-specific antibodies.⁸⁶ Treatment was for 2-3 years. Quinapril did not affect the number of new digital ulcers, nor did it affect Raynaud's severity or other vascular manifestations of SSc. Adverse affects occurred in one-fifth of the patients, with dry cough being the most frequent side effect.

In a double-blind placebo-controlled study of 11 patients with digital ischemic ulcerations, patients received either intravenous iloprost or saline infusions on 5 consecutive days.⁸⁷ Complete healing of all cutaneous ulcers was observed 10 weeks after treatment in 6 of 7 patients receiving iloprost versus none in the placebo group ($p=0.015$). Adverse effects such as nausea, vomiting, and headache were limited to the period of drug infusion and one patient withdrew because of chest pain. The authors concluded that iloprost might be useful for treating digital ulcers associated with SSc.

More recently, different dosages of iloprost were compared in the treatment of ulcer healing. Patients were randomized 1:1 to receive either 2 ng/kg/min or low-dose (0.5 ng/kg/min) iloprost for 3 weeks. Patients had 70% reduction of digital ulcers following either regimen. The

TABLE 35-2—Therapies for Digital Ulcers

Therapy	Outcome Measurement	Efficacy	Level of Evidence	Significant Changes	Reference
2% DMSO and 70% DMSO	Number of open ulcers Surface area of ulcers	0	1b	No significant differences found between treatment groups and placebo group	85
Quinapril	Reduction of new digital ulcers	0	1b	No significant differences found between treatment group and placebo group	86
Intravenous iloprost	Healing of cutaneous ulcers	++	1b	Significant decrease between iloprost and placebo groups	87
High-dose and low-dose iloprost	Reduction in digital ulcers	++	2b	No significant difference between treatment groups; 70% reduction in digital ulcers using either regimen	69
Teprotinil	Change in diameter of largest baseline ulcer	++	4	4/5 patients completing study experienced resolution of ulcer	88
Bosentan	Number of new digital ulcers	++	1b	Significant reduction in number of ulcers in bosentan group	89
Atorvastatin	Number and severity of digital ulcers	+	1b	Significant difference between atorvastatin and placebo groups; digital ulcer severity improved significantly in statin group	90
Local stem cell implantation	Vascular symptoms and ulcer healing	+	4	Ulcer healing and decreased pain	91

DMSO, dimethyl sulfoxide.

What We Know

- Design and interpretation of clinical trials for scleroderma is currently hampered by: lack of endpoints that are valid measures of disease activity; lack of validated diagnostic and entry criteria to study patients with very early disease; and lack of understanding of disease pathogenesis.
- Scleroderma skin disease does not tend to respond well to conventional doses of traditional immunosuppressants.
- High-dose immunosuppression followed by stem cell rescue is a promising therapy that appears to have dramatic efficacy for cutaneous sclerosis.
- Endothelin receptor antagonists are effective at preventing digital ulcerations in scleroderma.
- Prostacyclin analogues and phosphodiesterase-5 inhibitors are promising agents for the treatment of digital ulcerations but need to be tested in prospective, placebo-controlled clinical trials.

authors concluded that low-dose iloprost is just as effective as high-dose iloprost in the treatment of digital ulcers.

Treprostinil is a prostacyclin analogue approved in the United States for pulmonary arterial hypertension treatment. In a single-center, open-label study, treprostinil was further evaluated for the treatment of digital ulcers.⁸⁸ Patients with digital ulcerations secondary to systemic sclerosis received treprostinil infusion for 12 weeks up to a maximum rate of 15 ng/kg/min. The primary endpoint was change in diameter of a selected target lesion (the largest baseline ulcer). Twelve patients were enrolled but seven withdrew because of severe injection site pain, and two patients experienced gangrene of previously ischemic digits, which required amputation. Four of five patients that completed the study achieved primary endpoint, with complete resolution of target lesions by 12 weeks with no recurrence. Furthermore, the average diameter of digital ulcerations decreased for digital tip lesions and lesions overlying the joints. No patients developed new digital ulcerations during treprostinil therapy.

Treatment with the endothelin receptor antagonist bosentan was investigated for the treatment of digital ulcers in patients with SSc.⁸⁹ In a double-blind, placebo-controlled study (n=122) the number of new digital ulcers developing during a 16 week period was studied. Patients receiving bosentan for 16 weeks had a 48% reduction in the number of new ulcers during the treatment period and this difference was statistically significant ($p=0.0083$). In this study, fewer digital ulcers developed in patients treated with bosentan as compared to placebo group, but the p-value is not stated. The reduction in the number of new ulcers was most significant in patients who had ulcers at baseline and in those with diffuse SSc. There was no difference between the treatment groups in the healing of existing ulcers. In the treatment group, 14% of patients experienced elevation of serum transaminases to >three-fold the upper limit of normal, which is comparable to previous studies with bosentan.

Statins are thought to affect endothelial function and potentially slow vascular injury. Atorvastatin was studied in a randomized, double-blinded, placebo-controlled trial (n=84) of patients with Raynaud phenomenon and digital

ulcers.⁹⁰ The treatment group received 40 mg daily of atorvastatin for 4 months. The overall number of digital ulcers was significantly reduced in the statin group (1.6 new ulcers per patient in the treatment group as compared to 2.5 in placebo). Digital ulcer severity also improved significantly in the statin group.

Local stem cell implantation was studied in two SSc patients with nonhealing digital ulcers.⁹¹ Local injections of CD34+ cells from the peripheral blood and bone marrow were used for skin ulcers in the hands in each patient, respectively. The CD34+ cells from bone marrow and peripheral blood showed a rapid beneficial effect on vascular symptoms leading to ulcer healing and decreased pain. The efficacy was associated with restoration of endothelial function and increasing microcirculatory blood flow.

CONCLUSION

In the treatment of cutaneous SSc, many agents have been evaluated and failed, likely because the pathogenesis of scleroderma remains poorly understood. In addition, it is unclear how plastic many of the changes are in patients with well-developed disease. Unfortunately, once patients are diagnosed and thought suitable for clinical trials, many of the changes caused by fibrosis and vasculopathy may be irreversible. It is possible that many of the therapies reviewed here would be effective if applied in patients with very early disease—at this time diagnostic criteria do not exist to identify those patients. Thus, the future of therapy for this disease may indeed focus on prevention of progression, and will require both validation of novel diagnostic criteria for early disease as well as markers of skin activity that predict subsequent fibrosis.

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Treatment of Vitiligo

36

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INTRODUCTION

Vitiligo is a disorder of the pigmentary system, where individuals acquire sharply demarcated, depigmented macules in a localized or generalized distribution. These macules appear “milky white” as compared to the surrounding normally pigmented skin. The consensus definition proposed by the Vitiligo European Task Force (VETF) is as follows: “vitiligo vulgaris/NSV (nonsegmental vitiligo) is an acquired chronic pigmentation disorder characterized by white patches, often symmetrical, which usually increases in size with time, corresponding to a substantial loss of functioning epidermal and sometimes hair follicle melanocytes.”¹ This has sometimes been mistaken as leprosy and syphilis.

EPIDEMIOLOGY

This clinical entity occurs worldwide with an overall prevalence of 0.5-1%, and incidence ranges from 0.1 to >8.8%.² The highest incidence of vitiligo has been reported from India, followed by Mexico and Japan.² There does not seem to be a sex predilection and 70-80% of patients usually present before the age of 30.³ There is a positive family history of vitiligo in approximately 20-30% of patients, with data supporting a non-Mendelian, multifactorial, polygenic inheritance pattern.⁴

HISTORICAL BACKGROUND

Descriptions of white skin spots or patches have existed in ancient literature, dating back to at least 1500 BCE. Descriptions of these white spots have been interpreted as, but not limited to, leprosy and vitiligo. The origin of the word vitiligo is debated. Some suggest that the condition resembled the white glistening of the skin of calves (*vituli*), while others believed that it might be from the Latin word for calf, *vitellus*. Still, some believe that the word is derived from the Latin word *vitium*, meaning blemish. The term vitiligo is thought to have first appeared in the first century A.D., by Celsus, in his work *De Medicina*. In the text, translated from the Latin, Celsus writes:

Vitiligo also, though not dangerous in itself, is still ugly and is due to a bad habit of body. There are three species. It is called alphas when it is white in colour, generally rather rough, and not continuous, so that it looks as if drops of some sort had been sprinkled about. Sometimes also, it spreads still more widely with certain gaps. That called melas differs from it in being of a black colour and like a shadow; otherwise it is similar. Leuce is somewhat like alphas, but is whiter and extends deeper; there are hairs on it, white, and like down. All these spread, but more quickly in some people than in others. The alphas and melas come and go at various seasons; the leuce, once established, is not easily got rid of. The two former are not difficult to treat, the latter is scarcely ever cured, for even if the discoloration is mitigated, the colour of health does not right altogether.⁵

Interestingly, Celsus, as mentioned above divided vitiligo into three different subtypes: alphas, melas, and leuce; with none of them fully fitting the clinical definition of present day vitiligo.

PATHOGENESIS

Although the exact cause of vitiligo is not known, researchers have proposed a number of hypotheses to explain the characteristics of the disease. We will briefly review the most common theories.

Genetic Theory

Vitiligo patients are noted to have positive family histories in 6.25-30% of cases.⁶

Additionally, there have been some studies to suggest associations with HLA markers and vitiligo in different ethnic populations. Therefore, a genetic basis for vitiligo has been suggested.

Autoimmune Theory

Because there is complete absence of melanocytes in vitiligo macules, it has been proposed that there is immune destruction of these cells. Additionally, association of vitiligo with other autoimmune diseases has supported the

autoimmune nature. Dr. Lerner mentions in his 1959 paper on vitiligo, "there is evidence that the incidence of vitiligo is increased in hyperthyroidism, pernicious anemia, and Addison's disease. Patients with alopecia areata also are predisposed to development of vitiligo."³ Other evidence includes demonstration of autoantibodies in the sera against tyrosinase and tyrosinase-related proteins 1 and 2 (TRP-1 and TRP-2), T cell infiltrates in marginal skin, and abnormalities in peripheral mononuclear cells.⁶

Neural Theory

The neural theory was propounded by Lerner in his 1959 paper on vitiligo.³ He bases the hypothesis on four main clinical observations: (1) vitiligo has a segmental variant that presents unilaterally and is restricted to one portion of the body (seemingly along a dermatome), (2) vitiligo anecdotally occurs after a stressful event, (3) one patient with transverse myelitis, with paralysis from the waist down, developed vitiligo above the area of cord damage, not below and (4) he found autonomic dysfunction in patches of vitiligo. The theory suggests that nerve endings near melanocytes release a cytotoxic substance that destroys the melanocytes. Other evidence in support of this theory are the abnormalities of nerve growth factor and neuropeptides in nerve endings from perilesional skin.⁶

Self-destruction Theory

This theory suggests that abnormal accumulation of intermediaries of melanogenesis lead to death of melanocytes. This has been supported by the findings that: (1) derivatives of hydroquinone are capable of producing chemical leukoderma, and (2) abnormal pterin homeostasis may lead to elevated H₂O₂, decreased catalase activity, and increased pterin byproducts, causing melanocyte death.⁶

Growth Factor Defect Theory

This theory suggests that growth and maturation capabilities of melanocytes derived from vitiligo, may be defective. This may partially be reversed by the addition of growth factors.⁷

Convergence Theory

This theory suggests that the cause of vitiligo is multi-factorial and may represent a combination of the above-mentioned theories.⁸

CLASSIFICATION

Vitiligo has been classified a number of different ways, but a commonly used form is the following:

1. Localized
 - a. Focal – one or more macules in one area
 - b. Segmental – zosteriform or quasidermatomal pattern
 - c. Mucosal – only mucous membranes
2. Generalized
 - a. Acrofacial – hands/feet and face
 - b. Vulgaris – symmetrically scattered macules over entire body
 - c. Mixed (acrofacial, vulgaris, segmental)
3. Universal (>80% depigmentation)

TREATMENT

A literature search was done between July and November 2009 to identify randomized-controlled trials involving treatment for vitiligo. The studies of Whitton⁹, Gawkroger¹⁰, Njoo⁶, Forschner¹¹, and Falabella⁴ were extremely helpful in identifying papers for review. We took >75% repigmentation as the relevant outcomes for the papers. However, this was not possible in all cases because of the lack of statistical evidence.

Nonsurgical Repigmentation Therapies

Topical Treatments

WHAT IS THE EFFICACY OF TOPICAL STEROIDS VERSUS CONTROL FOR REPIGMENTATION IN VITILIGO?

One meta-analysis and one study was located that used topical steroids in a RCT, that of Kandil, in 1974.¹²

In the meta-analysis, the pooled odds ratio versus placebo for class 3 corticosteroids was 14.32 (95% CI, 2.45-83.72). Topical class 3 and 4 corticosteroids had the highest mean success rates for localized vitiligo (56%; 95% CI, 50-62% and 55%; 95% CI, 49-61%). Atrophy was the most common adverse effect for local corticosteroid therapy.⁶

In the second study, Kandil¹² randomized 19 patients to receive either 0.1% betamethasone valerate in 50% isopropyl alcohol or placebo (unmedicated base) twice daily on the left or right side of their bodies, for 4 months.

Both patients and investigators were blinded to treatment. Response was graded as repigmentation or cure versus no repigmentation. Two patients were lost to follow-up. Seventeen patients completed the trial. Fifteen of 17 lesions had repigmentation or cure in the treatment group, while 0/17 lesions had repigmentation.

After 4 months, six of 17 (35.3%) patients (9 patches) achieved >90% repigmentation, three patients received 25-90% repigmentation, and six patients were beginning repigmentation in the topical steroid group.

ADVERSE EFFECTS

Two patients in the Kandil study were lost to follow-up. Complications in the topical steroid treatment group

included hypertrichosis (2 patients) and a localized acneiform reaction (3 patients).

RECOMMENDATIONS

For localized vitiligo, topical corticosteroids seem to be effective, based on the meta-analysis. However, skin atrophy must be monitored as a potential side effect during treatment. The second study affirms that topical steroids can be somewhat effective in repigmenting vitiliginous skin.

WHAT IS THE EFFICACY OF TOPICAL STEROIDS VERSUS OTHER TREATMENT MODALITIES FOR REPIGMENTATION IN VITILIGO?

Four studies were identified that fit the criteria. Two of the studies, Khalid et al.¹³ and Lepe et al.¹⁴ examine the use of clobetasol in children versus either PUVA or tacrolimus. The other two studies compare betamethasone to either catalase/superoxide dismutase or calcipotriol. We will examine them in that order.

Fifty children under the age of 12 years old were randomly assigned to either treatment with topical 0.05% clobetasol propionate twice daily or topical 8-MOP followed by sunlight exposure (topical PUVA) thrice weekly for 6 months. After every 1.5 months of treatment, topical steroid holidays were given for 2 weeks.

Nine of 22 (40.9%) patients in the steroid group and two of 23 (8.7%) patients in the topical PUVA group achieved >75% repigmentation. Whitton et al. calculated a significantly better repigmentation in the steroid group, as compared to topical PUVA (RR 4.70; 95% CI, 1.14-19.39).⁹

The second clobetasol study, that of Lepe et al.¹⁴ compared 20 symmetrical, vitiliginous lesions after randomization for treatment to topical 0.05% clobetasol propionate or 0.1% tacrolimus twice daily or 2 months.

Treatment was double-blinded and monitored every 2 weeks. Results reveal percent repigmentation of 49.3% versus 41.3% in the clobetasol and tacrolimus groups, respectively. Greater than 75% repigmentation was seen in five of 20 (20%) lesions in both groups, which was not statistically significant.

The third study¹⁵ involved comparison of 0.05% betamethasone to topical catalase/dismutase superoxide in a randomized, double-blind trial. 25 patients, aged 12-74 years old, were randomly divided to the aforementioned treatments on symmetrical vitiligo lesions.

They found that there was no statistical difference in percent repigmentation between the two groups at 4 (5.63% ± 27.9 vs. 3.22% ± 25.8, $P = .758$) and 10 months of therapy (18.5 ± 93.14% vs. 12.4 ± 59%).

The last study is that of Kumaran et al.¹⁶ They randomized 49 patients into three groups: 0.05% betamethasone dipropionate cream (Group I), 0.005% calcipotriol

ointment (Group II), or betamethasone/calcipotriol combination (Group III).

They found that none of the patients, in either group, achieved >75% repigmentation. Time to repigmentation was significantly faster in Group III, as compared to the other two groups (Group I: 9.04 ± 2.0, Group II: 10.18 ± 1.6, Group III: 5.17 ± 2.4, $p < .01$)

ADVERSE EFFECTS

Khalid et al. had two patients experience blistering reactions in the PUVA group. Adverse events in the steroid group were mild atrophy (4 patients), telangiectasia (2 patients), hypertrichosis (1 patient), and acneiform papules (2 patients). Five patients were lost to follow-up.

Lepe et al. had two lesions in the tacrolimus group experience burning. Adverse reactions in the clobetasol group were: atrophy (3 lesions) and telangiectasia (2 patients).

Sanclemente et al. found that one patient had a mild, erythematous, popular rash that self-resolved.

Kumaran et al. found that four patients did not complete 3 months of treatment. Side effects in the steroid group occurred in seven of 15 patients and included lesional atrophy, lesional soreness, lesional dryness, and hypertrichosis. In the calcipotriol group, two of 15 patients side effects, including perilesional hyperpigmentation and irritant reaction. Side effects in the combination group (2/15) included: hypertrichosis and dryness of the skin.

RECOMMENDATIONS

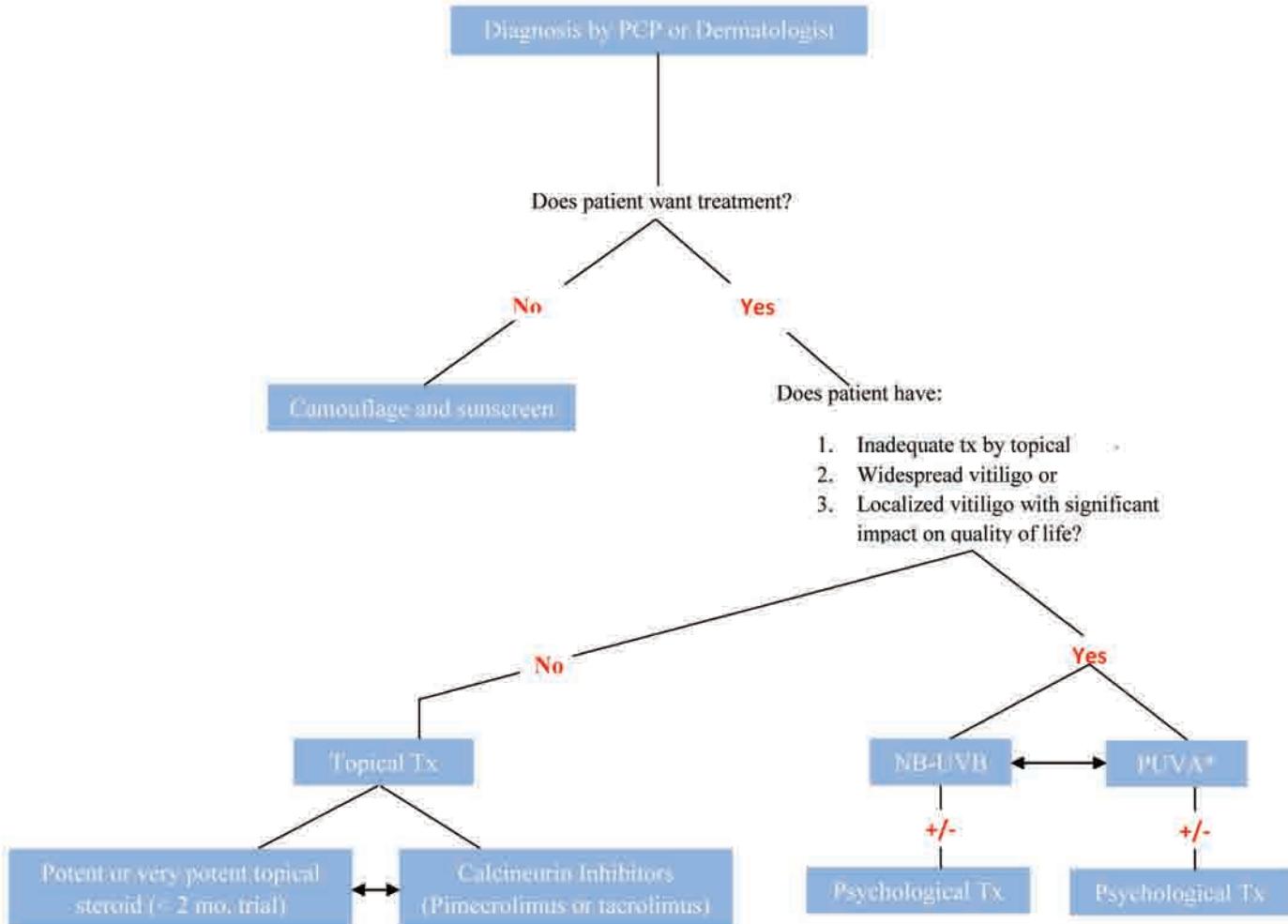
The only treatment that seemed to be inferior to topical steroid was PUVA. These studies reveal that some degree of repigmentation, with improved time to repigmentation may be achieved with topical steroids. However, the side effect profile of steroids tends to make their use more cautious. Steroids have been recommended for first line treatment of localized vitiligo by the meta-analysis of Njoo et al.⁶ However, the calcineurin inhibitors seem to have a safer side effect profile and may be used as alternatives.

WHAT IS THE EFFICACY OF INTRALESIONAL STEROIDS VERSUS CONTROL FOR REPIGMENTATION IN VITILIGO?

One study was identified, employing a randomized, placebo-controlled trial involving injections of 10 mg/mL triamcinolone acetonide suspension or distilled water. Thirty five patients were given weekly treatments for 8 weeks and then followed-up for 4 weeks.¹⁷

Results show that 17/25 (68%) patients in the treatment group and six of 10 (60%) patients in the placebo group achieved a fair to excellent response. Whitton et al. recalculated the statistics to achieve a relative risk (RR) of 0.97 (95% CI, 0.60-1.58), meaning that there was no statistical difference between treatment and placebo groups.⁹

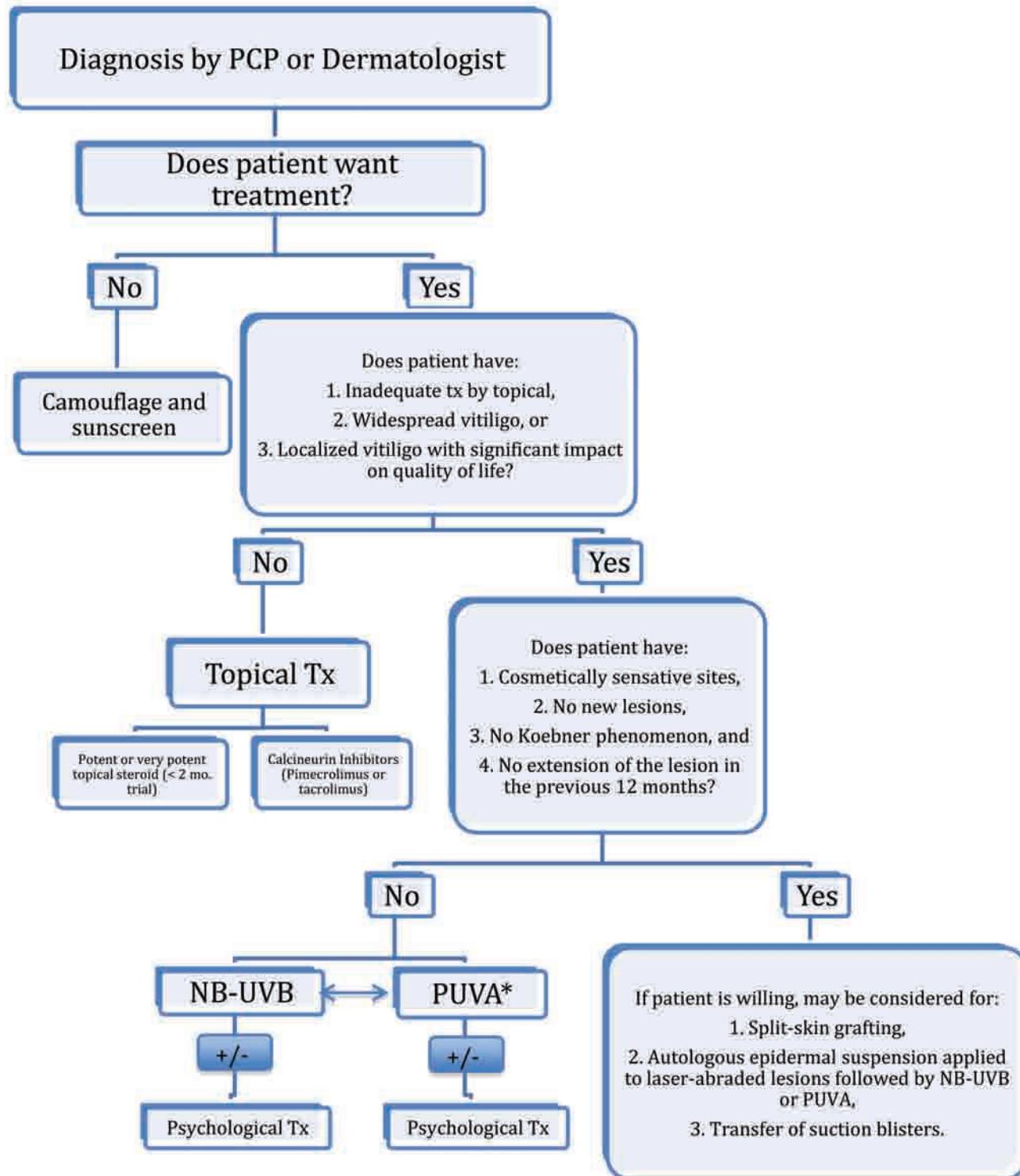
Vitiligo Treatment Algorithm in Children



* relative contraindication for those < 10 years old

FIGURE 36-1 Treatment algorithm for children adapted from Gawkroger DJ, Ormerod AD, Shaw L, et al. Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 2008;159:1051–76.

Vitiligo Treatment Algorithm in Adults



*Absolute contraindications: systemic lupus erythematosus, previous melanoma, dermatomyositis, xeroderma pigmentosum.

Relative contraindications: Pregnancy, previous non-melanoma skin cancer, current pre-malignant skin condition, cataracts (oral psoralen only)

FIGURE 36-2 Treatment algorithm for adults adapted from Gawkrodger DJ, Ormerod AD, Shaw L, et al. Guideline for the diagnosis and management of vitiligo. *Br J Dermatol* 2008;159:1051–76.

ADVERSE EFFECTS

In the treatment group, adverse effects were as follows: atrophy (8 patients), telangiectasia (2 patients), infection (1 patient), and intradermal hemorrhage (1 patient). The placebo group remained free of adverse effects.

RECOMMENDATION

Based on this one study, a case cannot be made for the use of intralesional steroids.

WHAT IS THE EFFICACY OF CALCINEURIN INHIBITORS VERSUS CONTROL FOR REPIGMENTATION IN VITILIGO?

Two RCTs were identified: One that looked at pimecrolimus and one that looked at different dosings of tacrolimus.

The first is that of Dawid et al.¹⁸ who examined the efficacy of 1% pimecrolimus cream versus placebo. They randomized 20 patients in a left-right manner, to receive treatment twice daily for 6 months. Outcomes measured were size of target lesion and repigmentation at 6 months. Both investigators and patients were blinded to treatment.

They found that 1% pimecrolimus resulted in no significant change in mean target lesion size. Additionally, patients in both groups did not achieve pigmentation >25%. At 6 months, three of 14 in the pimecrolimus groups and two of 14 in vehicle group had 1-25% repigmentation.

The second study¹⁹ looked at 0.1% tacrolimus, evaluating the efficacy of once or twice daily dosing, as opposed to a control lesion, for 6 months. Seventeen patients with generalized vitiligo were randomized for treatment. Fifteen patients with 40 target lesions completed the study. They found that only two lesions (13%) showed >75% repigmentation. In addition, analysis revealed a significantly better treatment outcome for twice-daily tacrolimus than for the untreated control ($P = 0.016$). Only one patient had 26-50% repigmentation in the control group.

ADVERSE EFFECTS

In the first study, four patients did not complete the study because of personal reasons (1 patient), presumed lack of efficacy (2 patients), and lost to follow-up (1 patient). No adverse effects were noted.

The second study lost two patients to follow-up, with reasons unexplained. No mention of adverse effects was made.

RECOMMENDATIONS

From these studies, it seems that topical calcineurin inhibitors may induce pigmentary responses, but not great enough to achieve >75% repigmentation. They may be tried because of favorable side effect profile.

Phototherapy

WHAT IS THE EFFICACY OF NARROWBAND UVB MONOTHERAPY VERSUS CONTROL IN VITILIGO?

Despite the presence of a good number of studies involving the use of UVB, only one study was found comparing narrowband UV-B (NB-UV-B) to control. In the study by Hamzavi and his group in 2004,²⁰ a prospective, coin-toss randomized, left-right controlled comparison trial was done on 22 vitiligo patients. Inclusion criteria included symmetric involvement, >5% total body surface area involvement, >18 years old, no significant medical problems, no treatment with a photosensitizing agent, and no topical or systemic treatment for 2 weeks prior to start of the therapy or during treatment. The side of the body exposed to NB-UV-B was randomly chosen, with the contralateral body half covered with a UV proof gown ("no light exposure"). If the face was included, it was treated completely. Therapy commenced thrice weekly for 6 months or 60 cumulative treatments, whichever came first. They measured body surface area vitiligo involvement, monthly, using their own quantitative tool, the Vitiligo Area Scoring Index (VASI). Additionally, total body photography was done monthly for validation of the VASI. They found that the extent of repigmentation in the NB-UV-B was 42.9% (95% CI, 26.7%-59%) versus 3.3% (95% CI, -19.3%-30.0%) on the untreated side ($P<.001$). They found the legs, trunk, and arms more likely to pigment than the feet and hands.

A meta-analysis of the literature by Njoo et al. in 1999⁶ revealed NB-UV-B therapy to be the safest and most effective therapy (63% success rate, 95% CI, 50-76%) for generalized vitiligo (>2% depigmentation) over a 6-24 month course.

ADVERSE EVENTS

According to Hamzavi et al.²⁰ hyperpigmentation of newly repigmented skin occurred, in addition to mild phototoxic effects. Hyperpigmentation resolved within the 6-month period for all patients in which it occurred. One patient dropped out of the study because of hyperpigmentation. However, the authors state that "twenty-two patients were recruited and treated from July 2000 to February 2001, and all were included in the analysis," creating confusion as to whether the dropped out patient's data was used.

RECOMMENDATIONS

There is a paucity of data from randomized clinical trials to be able to make firm statements in regards to clinical practice. However, the meta-analysis, by Njoo et al. points to the fact that NB-UV-B, as monotherapy, is the safest and least harmful treatment in generalized vitiligo.

WHAT IS THE EFFICACY OF PUVA SOL VERSUS CONTROL FOR REPIGMENTATION IN VITILIGO?

In the evaluation of research involving oral or topical psoralens with subsequent exposure to sunlight, three studies were found that were randomized-controlled clinical trials. The first study, by Pathak et al.²¹ in the 1980s, began as a double-blind, randomized-controlled trial with placebo, but had the placebo group terminated after 9-12 months of treatment for ethical reasons. They initially began with 566 East Indian patients, but had 366 patients complete the study and undergo analysis after 2 years. The patients were divided into 9 treatment groups with varying oral doses of the following compounds plus sunlight exposure: 8-methoxypсорален (8-MOP), 4,5,8-trimethylpsoralen (TMP), psoralen, or placebo. The groups were divided as follows: (1) 0.3 mg/kg 8-MOP, (2) 0.6 mg/kg 8-MOP, (3) 0.8 mg/kg TMP, (4) 1.8 mg/kg TMP, (5) 3.6 mg/kg TMP, (6) 0.3 mg/kg 8-MOP + 0.6 mg/kg TMP, (7) 0.6 mg/kg psoralen, (8) 1.2 mg/kg psoralen, and (9) placebo.

Patients were exposed to the sun, 2 hours after oral ingestion of the drug or placebo, for 45-60 minutes in gradually increasing doses between 11 a.m. and 2 p.m. thrice weekly. Patients were photographed approximately every 6 months during the 2-year treatment period. Repigmentation was measured as the outcome, with overall repigmentation expressed as a percentage of body surface area. The body was divided into different regions for analysis, including the face, head and neck, trunk, arms and legs, lips, hands, feet, palms and soles. Overall, the greatest pigmentation was achieved by the combination of 8-MOP and TMP at 38%, followed by the lower 0.3 mg/kg 8-MOP dose at 31%, and then the higher 0.6 mg/kg 8-MOP dose at 25%. The face, followed by the head and neck, showed the greatest response to treatment and the hands, feet, palms, and soles showed the worse responses, respectively. Almost half of the total number of patients in the 8-MOP/TMP combination and low dose 8-MOP groups achieved full repigmentation of the face, and 60% of the two groups achieved 75-100% repigmentation of the head and neck. Lastly, they found that the 8-MOP/TMP combination group had a statistically significant 19 fold greater rate of successful repigmentation (defined as 75-95% repigmentation response) as compared to placebo (RR 19.20; 95% CI 1.21-304.5). However, this must be viewed with caution for two reasons: (1) we previously mentioned that the placebo group did not complete the study, (2) the confidence intervals for the combination group, as compared to placebo, is wide.

A second study, by Maldonado et al,²² was published in the Spanish literature in 1975. This study employed a randomized, placebo-controlled design, on 50 children, lasting 8 months. Children were given oral trimethylpsoralen in doses ranging from 10-30 mg/day and then exposed either to a sun lamp or to sunlight. Those exposed to the

sunlamp received the TMP 3 hours before exposure, while those randomized to receive sunlight took one dose of TMP after breakfast and the other after lunch. Children randomized to the placebo group received their doses in a fashion similar to the treatment group. Exposure ranged from 3-30 minutes daily until erythema appeared. Patient pigmentary improvement was graded as slight, marked, or clinically cured. They found that the children in the TMP + sunlight/sunlamp group were two times more likely to achieve improvement than those in the placebo + sunlight/sunlamp group (RR 2.29; 95% CI 1.14-4.58).

The third study is the randomized, controlled trial of Farah et al.²³ published in 1965. They enrolled 88 patients and randomly divided them into four groups: (1) oral psoralen + sunlight, (2) topical psoralen + sunlight, (3) oral 20 mg methoxypсорален/8-12 mg triamcinolone daily + sunlight, (4) no treatment or dihydroxyacetone for cosmetic effects. Patients in the treatment groups were exposed to sunlight at midday, 2 hours after ingestion or directly after topical application of the treatment. Thirty-four of 61 patients in the treatments groups were followed up, with the fate of those who were lost to follow-up being unexplained. The number of patients who finished the study in the nontreatment/dihydroxyacetone group was not disclosed. Outcomes were graded as "good" or "none," with "good" meaning >50% repigmentation in the vitiliginous patches. A "good" response to treatment was found as follows: two of nine in the oral psoralen group, two of 10 in the topical psoralen group, 14/15 in the oral methoxypсорален/triamcinolone group, and none in the non-treatment group. The response in the combination group took 3-4 weeks to become evident, with some continuing treatment for 7 months. This study did not employ rigorous statistical analysis and details of patient demographics are lacking.

Lastly, the meta-analysis by Njoo et al.⁶ demonstrated odds ratios for oral 8-MOP, TMP, and psoralen individually, plus sunlight versus placebo as 23.37 (95% CI, 1.33-409.93), 3.75 (95% CI, 1.24-11.29), and 19.87 (95% CI, 2.37-166.32) respectively. This meta-analysis included the results from the above three studies of Pathak et al. Maldonado et al. and Farah et al.

ADVERSE REACTIONS

Forty-nine percent of all patients, in the Pathak et al. study reported side effects. Side effects included: nausea, pruritus, dizziness, headaches, eye discomfort, and gastrointestinal symptoms. The group reporting the highest number of side effects was the combination 8-MOP/TMP group.

Maldonado et al. had three children in the placebo group withdraw from the study.

Lastly, the study of Farah et al. does not make mention of adverse reactions or reasons for withdrawal from the study. The author writes that "the results are recognized as preliminary and do not include prolonged follow-ups."

RECOMMENDATIONS

From the above studies, it can be said that PUVA may be effective in repigmentation, but its results and side effects are difficult to control. Therefore, NB-UVB, or PUVA is preferred over PUVA.

WHAT IS THE EFFICACY OF ORAL OR TOPICAL PUVA VERSUS CONTROL FOR REPIGMENTATION IN VITILIGO?

Unfortunately, there are no identified randomized clinical trials comparing oral or topical PUVA with controls. However, the meta-analysis of Njoo et al.⁶ describes a success rate of 51% (95% CI, 46-56%) for oral methoxsalen and UV-A in generalized vitiligo.

ADVERSE REACTIONS

Njoo et al. state that oral methoxsalen and UV-A resulted in the highest rates of adverse effects, including: (1) nausea and vomiting in 29% (95% CI, 24-35%), and (2) phototoxic reactions in 25% (95% CI, 20-30%).⁶

RECOMMENDATIONS

Randomized, clinical trials involving oral or topical PUVA versus placebo for the treatment of vitiligo are lacking in the literature. However, if we examine the meta-analysis of Njoo et al.⁶ we may say that oral PUVA is the third most effective treatment in generalized vitiligo, following narrowband UV-B and broadband UV-B.⁶ However, there are greater side effects with PUVA treatment as compared to all other treatments.

WHAT IS THE EFFICACY OF NARROWBAND UV-B VERSUS ORAL PUVA FOR REPIGMENTATION IN VITILIGO?

Although there are a number of studies comparing narrowband UV-B to oral PUVA, including those of Westerhoff et al. Bhatnagar et al. and el-Mofty et al. they do not fit the criteria for randomized-controlled trials. The only study found to be a RCT was that of Yones et al. published in 2007.²⁴

Fifty-six patients were recruited and randomly divided into two treatment groups: (1) 25 mg/m² 8-MOP or 50 mg/m² 5-MOP (if the patient had nausea with 8-MOP) + UVA, or (2) placebo + NB-UVB. Both observers and patients were blinded to treatment and the patients received therapy twice weekly.

NB-UVB was started at a dose of 0.1 J/cm² and PUVA at 0.5 J/cm². Patients had body surface area (BSA) involved with vitiligo assessed at commencement and after every 16 sessions, using a Wood's lamp and photography. Participants also completed Dermatology Life Quality Index (DLQI) and visual analog scale (VAS) questionnaires

during the assessments. Outcomes measured were the change in BSA affected by vitiligo and the color match of the repigmented skin compared with unaffected skin after 48 treatments, at the end of therapy, and 1 year after the end of therapy.

Twenty-five patients in each group were included in the final analysis. The median number of treatments in the PUVA group was 47, compared to 97 in the NB-UVB group ($z = 2.1; p = 0.3$). In regards to BSA repigmentation, they looked at improvement at the end of treatment and after 48 treatments (for those who completed that many treatments). At the end of treatment, they found that 16/25 (64%) of patients in the NB-UVB group versus 9/25 (36%) in the PUVA group showed greater than 50% improvement in BSA repigmentation. Although the NB-UVB group tended to produce greater repigmentation than the PUVA group, this trend lacked significance ($p = .06$). After 48 treatments, there was a statistically significant increased efficacy for greater than 50% BSA repigmentation in the NB-UVB (11/21, 53%) versus the PUVA group (3/13, 23%) ($z = 2.3; p = .007$). If we were to take successful repigmentation to mean >75%, as done in the Cochrane review by Whitton et al. we find that at the end of treatment, five of 25 (20%) showed successful repigmentation in the PUVA group and eight of 25 (32%) in the NB-UVB group. In those completing 48 treatments, we find 0/13 (0%) in the PUVA group and one of 21 (5%) in the NB-UVB group with >75% repigmentation. Lastly, repigmentation color match was excellent in all of those in the NB-UVB group, but only in 11 patients (44%) in the PUVA group. ($\chi^2_1 = 19, P < .001$). At the end of the 1 year follow-up, the color match of all patients in NB-UVB group remained excellent, but was excellent in only 14/23 patients (61%) of the PUVA group (NB-UVB vs. PUVA: $\chi^2_1 = 12, P < .001$).

ADVERSE REACTIONS

Firstly, of the 56 patients that were initially recruited (28 in each group), three patients from each group did not commence treatment, for unknown reasons. Secondly, of the 25 patients in the PUVA group, eight patients (32%) had to be switched from 8-MOP to 5-MOP because of nausea. Thirdly, erythematous reactions were classified as Grade 1, just perceptible, or Grade 2, easily perceptible but causing no symptoms or only mild discomfort. The median number of erythema episodes was 9 in the PUVA group and 2 in the NB-UVB group ($z = 3.7, P < .001$). Seven of eight Grade 2 erythema reactions overall were in the PUVA group, with one patient in the PUVA group discontinuing treatment because of adverse effects, as compared to none in the NB-UVB group. Lastly, although the authors did not consider a hyperpigmentary repigmentation to PUVA an adverse effect, they found that 12 patients in the PUVA group had repigmentation that was noticeably darker than unaffected skin.

RECOMMENDATIONS

This study is the first RCT to effectively demonstrate that NB-UVB is superior to PUVA in terms of side effects, efficacy of repigmentation, color match of repigmentation, and efficacy 1 year post-treatment. However, their >75% repigmentation efficacy rates seem lower than previously published data (NB-UVB: 63% success rate, 95% CI, 50-76%; oral methoxsalen + UVA: (51% success rate, 95% CI, 46-56%) for either modality individually.⁶ However, the authors add that NB-UVB is more favorable than PUVA because of no need for oral medication, lack of need for eye protection post-treatment, it may be used in pregnancy, is not contraindicated in hepatic impairment, or for those on warfarin or phenytoin, and has less potential for development of skin cancer.

WHAT IS THE EFFICACY OF THE EXCIMER LASER (308 NM) VERSUS PLACEBO FOR REPIGMENTATION IN VITILIGO?

There is only one RCT, to our knowledge, that compared the 308 nm excimer laser with control lesions. The study of Passeron et al.²⁵ compared topical 0.1% tacrolimus + 308 nm excimer laser with 308 nm excimer laser monotherapy.²³ However, as part of the excimer laser monotherapy, the investigators compared symmetrical, untreated, control lesions on the opposite side.

In the study, 14 patients, age 12-63 years old, had 4 to 10 target lesions chosen (2-5 vitiliginous macules treated by the combination either therapy or laser monotherapy and 2-5 untreated vitiliginous macules on the opposite side). The treatment applied to each target lesion was randomly selected by drawing lots and treated twice weekly, for a maximum of 24 sessions. Repigmentation was graded on a 0-5 scale as follows: 0 – no repigmentation, 1 – 1-24% repigmentation, 2 – 25-49% repigmentation, 3 – 50-74% repigmentation, 4 – 75-99% repigmentation and 5 – total repigmentation. Efficacy was evaluated by two blinded, independent physicians.

They found that no repigmentation occurred in the untreated, control areas, while 17/20 lesions (85%) in the excimer only group showed repigmentation. However, only four of 20 (20%) lesions showed greater than 75% repigmentation in the excimer only group, which was not statistically significant compared with untreated lesions ($P = .15$). The authors state that the lack of statistical significance may be attributed to small sample size.

ADVERSE EVENTS

All patients experienced moderate to severe erythema at least once, and four lesions (2 in excimer alone group) had localized bullous eruptions.

RECOMMENDATIONS

The excimer laser is a relatively newer treatment, used since 2001 for the treatment of vitiligo. From this study, it seems that the excimer laser is effective in causing repigmentation. However, the extent of repigmentation may not be cosmetically adequate. It may be that repigmentation will increase with the number of treatments. It has the advantage of selectively targeting vitiliginous lesions, sparing unaffected skin. More studies are needed to adequately identify its role in vitiligo therapy.

WHAT IS THE EFFICACY OF NB-UVB VERSUS 308 NM MONOCHROMATIC EXCIMER LIGHT FOR REPIGMENTATION IN VITILIGO?

One RCT was identified, by Casacci et al.²⁶ that compared the 308 nm monochromatic excimer light (MEL) with NB-UVB.²⁴ They conducted the study in two centers, one in Italy, the other in France. A left-right randomized, investigator-blinded trial was undertaken with 21 vitiligo patients. Patients ranged from 16-58 years old, with a median age of 38 years old, and varied from skin types II-IV. Corresponding vitiliginous lesions on opposite sides of the body were randomized to receive either NB-UVB or the 308 nm MEL.

Treatment started at 70% of the minimal erythema dose (MED), determined prior to study commencement, and comprised of twice-weekly treatment for 6 months. Treatment was evaluated via clinical examination and photography at baseline and twice monthly. Repigmentation was graded from 0-4 with the score divided as follows: 0-no repigmentation, 1-poor repigmentation ($\leq 25\%$), 2-moderate repigmentation (26-50%), 3-good repigmentation (51-75%), 4-excellent repigmentation (76-100%). Five patients did not complete the study, leaving 16 patients that were included in the results. Lesions with >75% repigmentation included 6/16 (37.5%) in the 308 nm MEL group and 1/16 (6%) in the NB-UVB group. Bilateral areas chosen for treatment included 7 elbows, 4 knees, 2 backs, 1 neck, 1 axillae, and 1 lower limb.

The mean repigmentation score was significantly higher for the 308 nm MEL compared with NB-UVB (2.68 ± 1.35 vs. 2.12 ± 1.02 , $P = .04$). There was no statistically significant difference in treatment time required to achieve follicular repigmentation; however, there was a significant difference for peripheral repigmentation (308 nm MEL: 22.46 ± 8.25 , NB-UVB: 27.63 ± 9.37 ; $P = .0066$). The cumulative UV dose was also significantly lower in the 308 nm MEL group as compared to the NB-UVB group (38.97 ± 4.83 J/cm² vs. 59.43 ± 15.35 J/cm²; $P < .0001$).

ADVERSE EFFECTS

The authors state that symptomatic erythema occurred in nine of 16 (56.2%) patients during the first 12 treatments.

However, they do not state within which groups the erythema occurred. They do state that the side effects were similar between the groups. Five patients did not complete the study, with noncompliance given as the most common reason. No patients experienced blistering reactions.

RECOMMENDATIONS

The 308 nm MEL has at least similar efficacy as NB-UVB in the treatment of localized vitiligo lesions, in this study. There seems to be a faster time to peripheral repigmentation, with lower cumulative UV doses with the 308 nm MEL. Additionally, for localized vitiligo, there is the advantage of avoiding treatment of unaffected skin.

WHAT IS THE EFFICACY OF NB-UVB VERSUS NB-UVB COMBINATION THERAPIES FOR REPIGMENTATION IN VITILIGO?

NB-UVB VERSUS NB-UVB + ORAL ANTIOXIDANTS

Three RCTs were identified that compared conventional NB-UVB to NB-UVB combination therapy with oral antioxidants. The study of Dell'Anna et al.²⁷ combined NB-UVB with an oral antioxidant pool (AP) (α -lipoic acid, vitamins C and E, polyunsaturated fatty acids, and cysteine monohydrate), while that of Middelkamp-Hup et al.²⁸ combined NB-UVB with oral polypodium leucotomos extract, and Elgoweini et al.²⁹ combined NB-UVB with oral vitamin E. We will examine the studies in the above order.

Dell'Anna et al. employed a randomized, double-blind, placebo-controlled, multicenter trial, dividing 35 patients with generalized vitiligo into NB-UVB + placebo or NB-UVB + AP (50 mg α -lipoic acid, 50 mg vitamins C, 20 mg vitamin E, 12% polyunsaturated fatty acids, 50 mg cysteine monohydrate) groups. Patient age ranged from 24–61 years old, with a mean of 39.9 years. Patients began taking 2 tablets of the oral supplements daily 2 months before commencement of NB-UVB therapy, and continued for 6 months during concurrent phototherapy. NB-UVB was administered twice weekly, with a starting dose of 70% of the MED (of unaffected skin).

Two blinded investigators assessed the participants for size and number of lesions at a screening visit before therapy, after 2 months of placebo or AP but before commencement of NB-UVB, and at the end of 6 months of concurrent treatment. Patients were photographed and repigmentation was graded on a scale of 0–3: 0-absent, 1-moderate (< 50%), 2-good (51–75%), 3-excellent (>75%) for each lesion. Additionally, blood was drawn during the assessments and analyzed for peripheral blood mononuclear cell (PMBC) redox status. Twenty-eight of the 35 patients completed therapy with full compliance and were included in analysis.

The investigators found that eight of 17 (47%) of the patients in the NB-UVB + AP group, compared with 2/11

(18%) in the NB-UVB + placebo group, developed >75% repigmentation ($p <.05$). Best responses were noted on the face, neck, and proximal limbs. The average number of treatments to achieve >50% repigmentation was 18 in NB-UVB + AP group compared to 23 in the NB-UVB + placebo group. In terms of redox status, they found that both catalase activity was significantly higher (164 ± 43 U/mg protein vs 139 ± 31 U/mg protein, $p <.05$) and reactive oxygen species (ROS) significantly decreased (60% from baseline, $p <.02$) in the AP group, as compared to the placebo group, at the end of therapy.

The second study, that of Middelkamp-Hup et al. was undertaken to investigate the antioxidative and immunomodulatory effects of the plant extract, *polypodium leucotomos*, on vitiligo. Fifty patients, aged 22–65, with vitiligo vulgaris were randomly assigned to receive 250 mg of oral *P. leucotomos* or placebo three times daily, combined with NB-UVB twice weekly for 25–26 weeks.

Both investigators and patients were blinded to treatment group. Assessment of repigmentation was done via clinical examination and photography at the beginning and end of the study. Patients, additionally, underwent vitiligo severity grading by the investigators and self-assessment, completed a survey on the effect of treatment on quality of life, and had blood drawn for cytokine analysis. One patient was lost to follow-up in the placebo group.

The study revealed that there was no significant difference in the treatment, compared with the placebo group, in percentage of repigmentation obtained at the end of the study. The mean cumulative dose was similar for both the treatment and placebo groups (49 J/cm^2 vs 52 J/cm^2). However, if the intention to treat analysis was abandoned and calculations were done for those who attended >80% of the phototherapy sessions, we find that the treatment group had statistically greater repigmentation than placebo in the head and neck area (50%; 95% CI 36–64 vs 19%; 95% CI 7–31; $P <.002$). Secondly, there was no significant difference was found in the change in quality of life between groups during their assessment. Lastly, no clear trends were observed in the detected cytokines in blood samples, with numbers too small to make conclusions.

The last study is that of Elgoweini et al. where 24 patients, aged 19–50 years, with stable vitiligo were divided randomly into two treatment groups. Group A included patients treated with NB-UVB + oral vitamin E (400 IU alpha-tocopherol) daily, starting 2 weeks prior to NB-UVB therapy (12 patients). Group B included patients treated with NB-UVB as monotherapy (12 patients). Both groups had NB-UVB therapy administered 3 times per week for 6 months.

Improvement was recorded at the beginning and end of treatment, by two independent observers, depending on the extent of repigmentation in the existing lesions. This was graded as none (0%), mild (1%–25%), moderate (26%–50%), marked (51%–75%), and excellent (>75%). Response

to the treatment was also evaluated by digital photography. Blood samples were drawn for analysis of lipid peroxidation (malondialdehyde [MDA]) and reduced glutathione (GSH). Three of 12 patients in the NB-UVB group and one of 12 patients in the NB-UVB + oral vitamin E group did not complete the study.

The investigators state that marked to excellent repigmentation (51-100%) of the vitiliginous lesions was noted in eight of 11 (72.7%) patients in group A and in five of 9 (55.6%) patients in group B. However, there is no statistical analysis of repigmentation percentages for significance. Additionally, the exact numbers of patients achieving >75% repigmentation are not clearly stated in the paper. They, further, claim that number of treatments needed to achieve 50% repigmentation was significantly less in Group A (16 treatments) compared with Group B (20 treatments), and Group A patients experienced less mild erythema (70%) compared to Group B (85%). Again, calculations of *p* values were not shown for these numbers. Lastly, a significant reduction in plasma malondialdehyde, a marker of lipid peroxidation, was found in Group A compared to Group B (*P* <.001).

ADVERSE EFFECTS

Dell'Anna et al. had seven of 35 (20%) patients drop out of the study. Reasons cited, according to the authors, were unrelated to therapy and included: fever, physical trauma, and job changes. They also stated that of those individuals who completed the study, adverse effects were minimal, with no patient requiring suspension or discontinuation of therapy. However, they did not elucidate the nature of the minimal effects.

Middelkamp-Hup et al. had one of 50 patients drop out of the study on the last visit for unknown reasons. Of the 49/50 that completed the study, 10/25 in the *P. leucotomos* group and five of 24 in the placebo group experienced transient itching. Additionally, five of 25 in the *P. leucotomos* group and three of 24 in the placebo group experienced dryness of the skin. Lastly, four of 25 in the *P. leucotomos* group and five of 24 in the placebo group experienced mild gastrointestinal complaints secondary to capsule intake.

Elgoweini et al. had one of 12 patients in the NB-UVB + oral vitamin E group and three of 12 patients in the NB-UVB group discontinue therapy. The authors stated that reasons for discontinuation were unrelated to treatment. Mild erythema was experienced by 70% of those in the NB-UVB + vitamin E group and 85% of those in the NB-UVB group.

RECOMMENDATIONS

From these three studies, it may be concluded that the evidence to support oral antioxidants as an effective adjunct to NB-UVB in the treatment of vitiligo is weak at

present, because of small patient numbers and employment of different antioxidants. It seems that the best responses were found in the facial region in all three studies. Effectiveness seemed to vary, based on the study, with the number of patients with greater than 75% repigmentation not being clearly described in one study, (Elgoweini et al.). Each study looked at different antioxidants or combinations of antioxidants, making comparison difficult. Further studies with a standardized repigmentation grading system are in order to further clarify the role of antioxidants in treatment.

NB-UVB VERSUS NB-UVB + TOPICAL

VITAMIN D₃ ANALOGUE

There are two identified RCT in the literature employing vitamin D₃ analogues: (1) NB-UVB + topical calcipotriol (Arca et al.)³⁰ and (2) NB-UVB + topical tacalcitol (Leone et al.)³¹ published in 2006.

The study of Arca et al.²⁸ enrolled 40 stable, nonsegmental vitiligo patients into two randomly assigned NB-UVB groups: (1) NB-UVB monotherapy (24 patients), and (2) NB-UVB + 0.05% topical calcipotriol twice daily (13 patients). NB-UVB was given three times weekly for 30 treatment sessions. Those in the topical calcipotriol group applied ointment after phototherapy. There was no placebo ointment and no mention was made of investigator or patient blinding.

Treatment was monitored by photography before the beginning and at the end of the treatment. Repigmentation was visually scored as: minimal (0-24%), moderate (24-49%) and marked to complete (50-100%). Thirty-seven of 40 patients completed the study and were included in the analysis.

They found that although both groups had statistically significant reductions in body surface area affected by vitiligo (NB-UVB: $27.21 \pm 10.41\%$ to $16.25 \pm 8.54\%$, *p* <.001; NB-UVB + calcipotriol: $23.35 \pm 6.5\%$ to $13.23 \pm 7.05\%$, *p* <.001) comparison of the reduction in repigmentation rates between the two groups showed no statistically significant difference (*P* > .05). The repigmentation was 50-100% for 10/24 (41.67%) patients in the NB-UVB group and 6/13 patients in the NB-UVB + calcipotriol group. This study did not employ >75% repigmentation as a clinical endpoint, and thus did not provide a breakdown of patients in that manner.

The second study randomly assigned 32 subjects, aged 18-54, with generalized vitiligo and symmetrical lesions to treatment with either NB-UVB or NB-UVB plus 4 µg/g tacalcitol applied daily. A left-right randomization was employed, with investigator blinding. Sixty four lesions were selected with locations on the face (12 pairs), axillae (10 pairs), elbows (5 pairs), knees (3 pairs) and forearms (2 pairs). NB-UVB therapy consisted of twice-weekly treatments for up to 6 months, starting with 70% of MED.

One investigator assessed repigmentation at the beginning and at the end of treatment, with photographs taken every 4 weeks. Repigmentation was scored 0-3 as follows: 0-none, 1-moderate (<50%), 2-good (50-80%), 3-excellent (>80%). Patients were also classified as “good responders,” “responders,” and “nonresponders.” However, the definition of the groups is not given in the paper.

The study showed that lesions treated with combination therapy showed significantly higher repigmentation scores than those with NB-UVB alone ($p<.0005$) at the end of the study. 16/32 (50%) lesions in the combination group versus 0/32 (0%) were scored as >80% pigmentation (score 3) at the end of 6 months of treatment. Lastly, those lesions in the combination group classified as “good responders,” (23 lesions) showed quicker onset of repigmentation compared with those in the NB-UVB group classified as “good responders” (23 lesions) (55 ± 25 days vs 130 ± 39 days).

ADVERSE EFFECTS

Arca et al. lost three of 40 patients (0.075%) in their study: one in NB-UVB group and two in the NB-UVB + calcipotriol group. The patients left for personal reasons. Individuals who completed the study experienced mild, transient itching or erythema as a side effect.

Leone et al. had no patients lost to follow-up. They state that the combination treatment was generally well tolerated, with side effects limited to mild erythema and itching. Of the 12 subjects treated on the face with combination treatment, most experienced mild irritation and desquamation following ointment application.

RECOMMENDATIONS

The top two studies present conflicting information with similar treatments. Arca et al. found no significant difference between treatment groups, while Leone et al. found the differences significant at all points during the study. The difference may be attributed to the first study examining repigmentation in the entire body, as opposed to the second study examining repigmentation in single lesions. No recommendations can be made based on the data.

NB-UVB VERSUS NB-UVB + TOPICAL TACROLIMUS

One randomized, placebo-controlled, double-blind trial was identified that compared NB-UVB with NB-UVB plus 0.1% tacrolimus ointment. This was done by Mehrabi and Pandya and published in 2006.³²

They recruited nine patients and randomly assigned paired vitiligo patches to either placebo (petrolatum) or treatment with 0.1% tacrolimus ointment twice daily, followed by NB-UVB three times weekly for 12 weeks. The starting dose was determined to be 70% of the minimal erythema dose for a patient with type 1 skin.

Blinded investigators examined the patients at 4-week intervals with concomitant photography of the target lesions. An image computer program was used to calculate the surface area affected by vitiligo in the target areas. Eight of the 9 patients completed the study.

They found that both sides had improved repigmentation overall. However, there was no statistically significant difference between the two groups (NB-UVB + placebo: 41.28% improvement versus NB-UVB, + tacrolimus: 49.24% improvement).

ADVERSE EFFECTS

One patient was withdrawn from the study at week 7 because she had missed nine of 20 NB-UVB treatments. The authors stated that common adverse effects reported by the 9 patients included redness (78%) and itching (89%). Less frequent complaints included non-specific blistering (44%) and a burning sensation (44%). Slight vesicle formation was noted on examination of two patients, resulting in withholding of 1 light treatment each and in the reduction of the next treatment dose by 10%.

RECOMMENDATIONS

This study did not show any benefit from tacrolimus in addition to NB-UVB. However, no definite recommendations can be made based on the results of this one study.

NB-UVB VERSUS NB-UVB + TOPICAL PSEUDOCATALASE

One randomized, double-blind, placebo-controlled trial was identified that investigated the utility of twice daily pseudocatalase cream in conjunction with NB-UVB versus NB-UVB plus placebo for 24 weeks. et al.³³

Thirty-nine patients were initially recruited and divided into treatment and placebo groups on an intention to treat (ITT) and per-protocol population (PPP) basis. Seven patients withdrew prior to commencement of the study. Patients applied either placebo or pseudocatalase to the entire body and received NB-UVB 10-30 minutes after application, three times weekly.

Patients were assessed during four visits: (1) initial screening, (2) extent of vitiligo assessed and photography of the hands and face done, (3) 12 weeks (photographs taken), (4) 24 weeks (photographs taken). Hand/face repigmentation analysis was done via digital photography and investigator assessment, while the whole body was only assessed by the investigator (without pictures). Fourteen patients in the treatment group and 18 patients in the placebo group commenced the study. Twelve of 14 patients in the treatment group and 13/18 patients in the placebo group completed the 24-week trial.

The analysis showed that there was no statistically significant difference between treatment groups on digital photography of the face and hands. There was a significant difference from baseline to the end of treatment, within groups, for the pseudocatalase group on the left and right face ($P = .0001$ and $P = .005$, respectively) and placebo group ($P = .003$ and $P = .01$)

ADVERSE EFFECTS

Seven patients withdrew prior to commencement of the study, with reasons cited as refusal to cooperate, screen failure, and going overseas. Another seven patients withdrew after commencement of the study: two in the treatment group and five in the placebo group. Reasons cited for withdrawal after commencement were, refusal to cooperate, personal reasons, and one adverse reaction (anxiety). The most common treatment-related adverse events were: pruritus, increased sweating, and thermal burns secondary to radiation therapy.

RECOMMENDATIONS

This study made use of pseudocatalase cream as an adjunct treatment. Assessment of efficacy; however, was mainly examined on the hands and face. Perhaps future studies should quantify repigmentation on the entire body. From this one study, a role for pseudocatalase, in addition to NB-UVB, has not been established.

NB-UVB VERSUS NB-UVB + VITAMIN B12/FOLIC ACID

The study of Tjioe et al.³⁴ explored the utility of vitamin B12 and folic acid as adjunctive treatments to NB-UVB. Twenty-seven patients, 20–68 years old, were randomized to receive NB-UVB or NB-UVB plus 1000- μ g vitamin B12/5 mg folic acid twice daily. Patients were given phototherapy 3 times a week, starting at 0.10 J/cm² and increasing by 0.30 J/cm², for 1 year. Assessment of repigmentation was accomplished by visual scoring monthly, and with before and after photographs. No placebo capsules were used during the study and there is no mention of investigator blinding.

They found that although NB-UVB was effective in repigmentation, there was no statistical difference between the two patient groups ($p \geq .175$). They further found that >90% repigmentation was found on the face, neck and throat, lower arm, chest, back and lower legs, while less than 25% repigmentation was seen on the hands, wrists, feet and ankles.

ADVERSE EFFECTS

Transient erythema was observed in all patients occasionally, although mild.

RECOMMENDATIONS

This study does not give repigmentation statistics in a written form, comparing the two groups. In addition, this study lacked a placebo control and investigator blinding was unclear. Based on this one study, clear recommendations cannot be made for use of vitamin B12/folic acid combinations in the treatment of vitiligo.

Surgical Repigmentation Therapies

Autologous Transplantation Techniques

WHAT IS THE EFFICACY OF NONCULTURED, AUTOLOGOUS EPIDERMAL CELL SUSPENSION TRANSPLANTS VERSUS PLACEBO FOR REPIGMENTATION IN VITILIGO?

A literature review revealed three RCT and one meta-analysis, to our knowledge, involving the use of noncultured, autologous epidermal cell suspension transplants for the treatment of vitiligo. We will examine these reports from oldest to most recent.

The first study if the meta-analysis by Njoo et Al.,⁶ published in 1999. They did a systematic review of autologous transplantation methods for the treatment of vitiligo. Their review does not make any mention of noncultured, autologous epidermal cell suspension transplants, but does mention that no conclusion can be made as to the efficacy of culturing techniques because of the small number of patient's studies.

The second study is that of Van Geel et al. published in 2004,³⁵ which was a prospective, randomized, double-blind, placebo-controlled, study on patients with generalized, and mostly stable vitiligo. They recruited 28 patients, aged 15–65 years old, with paired, symmetrically distributed lesions (33 pairs total) and randomly assigned them into two groups, after epidermal ablation (using pulsed CO₂ laser): (1) cellular suspension (melanocyte medium + hyaluronic acid + epidermal cells) and NB-UVB or PUVA or (2) placebo (melanocyte medium + hyaluronic acid) and NB-UVB or PUVA. Donor skin specimens for the cellular suspension were derived from the gluteal region. Lesions <4 cm² were treated in whole, while those >4 cm² had only a part of the lesion marked for treatment. For the first 2 weeks postprocedure, an occlusive dressing was placed and changed weekly. Treatment with either NB-UVB or PUVA, twice weekly, was commenced after the 3rd week, to stimulate melanocyte proliferation.

Efficacy of treatment was evaluated by percentage of repigmentation in the tested lesions. This was done by tracing the contours of the lesions and entering them into a computer for digital image analysis on the day of treatment and 3, 6, and 12 months after treatment. Repigmentation pattern was also noted at 1 and 3 months after treatment.

This study revealed that there was a statistically significant difference between groups at all time points. The

treatment group had >70% repigmentation of the treated area in 77% of the lesions 1 year after treatment. The placebo group did not have any lesions with >70% repigmentation at any time point. Lastly, the repigmentation pattern was diffuse (not perifollicular or peripheral) in 94% of responding lesions.

The third study is that of Tegta et al.³⁶ published in 2006, which compares two different dilutions of epidermal suspensions, containing differing numbers of melanocytes, over a 3-month period. They divided 22 patients, ranging from 10-54 years old, randomly into two groups: (1) suspension prepared from graft one-third size of recipient area (Group A), and (2) suspension prepared from graft 1/5 size of recipient area (Group B). Total melanocyte count of the suspensions was accomplished via a hemocytometer (Group A: 231.60 ± 27.03 melanocytes/mm²; Group B: 154.90 ± 27.65 melanocytes/mm²). The recipient site was prepared by blister formation, via suction, UVA, or liquid nitrogen spray, or a dermabrader if no blistering was used. Cellular suspensions were injected into blisters created at the lesions.

Assessment of the patients was carried out at 2, 4, 8, and 12 weeks. Efficacy was determined by degree of repigmentation, graded as no response, minimal (<25%), mild (26-50%), moderate (51-75%), and marked (>75%). Investigator/patient blinding was unclear. Twenty patients, 10 from each group, completed the study.

Differences in repigmentation, between the two groups, were found to be statistically significant at the end of the 3 months ($P < .05$). 5/10 (50%) patients in Group A and 0/10 (0%) of patients in Group B showed >75% repigmentation. Time to initial repigmentation was not statistically significant between the groups (Group A: 2.63 ± 5 vs. Group B: 3.00 ± 5).

The last study, that of Back et al.³⁷ published in 2009, was a randomized, placebo-controlled, study evaluating the use of a noncultured keratinocyte/melanocyte cosuspension in generalized vitiligo. They randomized 13 patients, aged 18-77 years old, into two groups: (1) melanocyte/karatinocyte cosuspension in Dulbecco's Modified Eagle's Medium (DMEM)/2% autologous serum, or (2) Dulbecco's Modified Eagle's Medium (DMEM)/2% autologous serum alone. The cell numbers were verified with a hemacytometer and the solutions were injected subcutaneously, after diamond-tipped burr dermabrasion.

Two outcomes were measured: (1) time to re-epithelialization (starting 3 days after procedure until complete healing), and (2) repigmentation of prepared areas (3, 6, 9, and 12 weeks and 6, 9, and 12 months thereafter). Both were assessed by a blinded investigator. Re-epithelialization was done visually, as was repigmentation. Repigmentation was also measured by a tristimulus colorimeter.

They found that there was no statistical difference in time to re-epithelialization between the two groups (median = 7 days in both groups, $P = .76$). Additionally, they found that five of 13 areas achieved normal pigmentation at

one time point, in the treatment arm, and two of 13 areas in the placebo group. However, of the 10/13 patients that followed-up at 12 months, 84% of the treated areas versus 100% of the placebo group displayed no pigmentation.

ADVERSE EFFECTS

Van Geel et al. had one patient in which there was doubt as to the original location of the test lesion, leading to exclusion from analysis and a second patient who left the country and was lost to follow-up. Erythema was seen in all lesions during the first 2 weeks, and gradually faded. Five patients experienced hyperpigmentation in the lesion, which gradually faded over 6 months. No scars were observed. They make mention of one patient with the Koebner phenomenon after treatment, but make no mention as to whether there was donor site involvement.

Tegta et al. had one patient lost to follow-up after developing a bacterial infection at the recipient site, two days after grafting. The patient was given systemic antibiotic treatment. Additionally, one patient had initial hypopigmentation in the donor area.

Back et al. had two areas develop slight infection, treated with topicals. They also had one subject develop severe hyperpigmentation at the donor site, persisting until the 1-year follow-up. Ten subjects suffered from a new leukodermic lesion at the donor site at the 1-year follow-up.

RECOMMENDATIONS

Two of the above-mentioned studies, Van Geel et al. and Tegna et al. provide evidence in favor of successful repigmentation with autologous cellular suspensions. The study of Back et al. provides evidence to the contrary. The difference in success may be the number of melanocytes transplanted. Tegna et al. had success with an average dilution of 231.60 ± 27.03 melanocytes/mm², and they recommended dilutions of 210-250 melanocytes/mm² for successful repigmentation. However, their study lacked a placebo group, but was added for interest. Van Geel's group also added either NB-UVB or PUVA to enhance melanocyte stimulation. Therefore, success is most likely operator dependent. Side effects of treatment include Koebnerization at the donor site, which was most evident in the study by Back et al. and infection at recipient or donor sites.

WHAT IS THE EFFICACY OF PUNCH GRAFTING FOR REPIGMENTATION IN VITILIGO?

One meta-analysis and two RCTs were identified that involved punch-grafting: one comparing punch-grafting plus topical corticosteroids versus punch-grafting plus PUVA, and the second comparing punch-grafting plus PUVA sol versus split-thickness skin grafting (STSG) plus PUVA sol. We will begin with the first study.

The meta-analysis of Njoo et al.⁶ shows punch-grafting to have the highest rate of adverse effects, including: donor site scar formation (40%, 95% CI, 34-47%) and recipient site cobblestoning (27%, 95% CI, 21-33%). However, it was shown to be a cheap and easy surgical method of repigmentation.

The second study, by Barman et al.³⁸ randomly divided 50 patients into two punch-graft groups, those who received PUVA twice weekly (group 1) and those who received topical 0.1% fluocinolone acetonide daily (group 2). Both adjuncts commenced 4 weeks post punch-grafting.

Treatment was monitored monthly for 6 months by photography and measurement of pigment spread. A total of 42 patients, 17 in group 1 and 25 in group 2, completed 6 months of therapy.

They found no statistical difference in pigment spread between the PUVA and topical steroid groups (mean at 6 months: 6.38 vs. 6.94, $P = 0.19$).

The third study is that of Khandpur et al.³⁹ which compared punch-grafting to STSG. Sixty-four patients were randomized into two groups: (1) punch-grafting plus PUVAsol or (2) STSG plus PUVAsol. They both started oral PUVAsol therapy (0.6 mg/kg/day, followed by sun exposure 2 hours later) after 2 weeks, on alternate days.

Assessment of treatment was done monthly for 3 months. Photography and visual repigmentation assessment were done at 3 months.

They found that 15/34 (44.1%) patients in the punch-graft group and 25/30 (83.3%) patients in the STSG group had >75% repigmentation after 3 months, which was statistically significant ($p < .001$). However, there is an internal discrepancy in the data of the paper which makes comparative analysis between study groups difficult.

ADVERSE EFFECTS

For Barman et al. six patients were lost to follow-up and two were excluded because of vitiligo reactivation. In group 1 (punch-graft + PUVA), seven patients experienced nausea and vomiting, six had cobblestoning, four had erythema and depigmentation of the graft, one patient had a pyogenic infection, and one had perilesional hypopigmentation, itching, scaling, and thickening of the skin. In group 2 (punch-grafting + topical steroid), five patients had polka-dot appearance, four had cobblestoning and atrophy of grafted area, three had graft depigmentation, and one had infection, perilesional hypopigmentation, and erythema.

Khandpur et al. had 81 punch-graft rejections (12.57%), cobblestoning (13/34, 38.23%), variegated appearance (7/34, 20.58%), and superficial scarring at the donor site in all cases in group 1. Group 2 patients experienced achromic fissuring (4/30; 13.3%), four graft contractures in three patients (2.61%), and rejection of seven grafts (4.57%) in one case; tire-pattern appearance in two patients (6.6%); milia formation in four (13.3%); and depigmentation of the grafts in 2 (6.6%) cases. Superficial and hypertrophic

scarring also occurred at the donor site, in all and three patients respectively.

RECOMMENDATIONS

Both of the above studies are comparing different treatment modalities. Blinding for these procedures may not be done for technical reasons. Punch grafting has not been compared to placebo in a RCT, to the best of our knowledge. PUVA or topical steroids do not seem statistically different effects, as adjuncts to punch grafting. In addition, STSG seems to be a better option, than punch grafting in terms of cosmetic appearance (prevention of cobblestoning), using fewer grafts, and enabling coverage of larger areas, as stated by the Khandpur et al. These few studies do not allow firm recommendations to be made for clinical practice.

WHAT IS THE EFFICACY OF SPLIT-THICKNESS SKIN GRAFTING VERSUS SUCTION BLISTERING FOR REPIGMENTATION IN VITILIGO?

The meta-analysis of Njoo et Al.,⁶ make mention of both of these surgical modalities. There was also one RCT identified, that examined STSG versus suction blistering.

Njoo et al.⁶ state that the highest mean success rates were achieved with STSG (87%; 95% CI, 82-91%) and epidermal blister grafting (87%; 95% CI 83-90%).

The study of Ozdemir et al.⁴⁰ randomly divided 20 patients, aged 10-49 years old, into two groups: those treated with STSG and those treated with suction blistering. STSG were taken from the gluteal area.

Two of three investigators were blinded to treatment. They followed the patients every 2 weeks for 3 months to assess repigmentation and adverse effects.

They found that repigmentation rates were 25-65% in the suction blister technique and 90% in the STSG technique ($P < .001$) after 3 months. However, they make no mention as to the percentage of repigmentation.

ADVERSE EFFECTS

Ozdemir et Al.,³⁸ found that the donor sites experienced Koebner phenomenon, hypopigmentation, hyperpigmentation, scarring, and infection. The recipient sites experienced milia, pigment loss, papule development, peripheral hypopigmentation, scarring, and infection.

RECOMMENDATIONS

The study results were difficult to interpret and the derivation of the repigmentation rates is not clear. They make no mention of percent repigmentation in the areas grafted. The side effects noted above warrant caution in using these surgical therapies, without full patient consent. Additional studies will be necessary to improve on existing techniques.

What We Know

- Topical Treatments: We know from RCTs that topical steroids are more effective than placebo; however, their effects are not statistically different from catalase/dismutase superoxide, tacrolimus, or calcipotriol. Steroids do seem to be more effective than PUVA. For localized vitiligo, topical corticosteroids seem to be effective, based on the meta-analysis. However, skin atrophy must be monitored as a potential side effect during treatment.
- Phototherapy: We can conclude that NB-UVB performs better than PUVA in terms of efficacy and side effect profile. Various adjuncts have been used with NB-UVB with varying results. The excimer laser may

- be as effective as NB-UVB, with the advantage of sparing unaffected skin.
- Surgical Treatments: Split-skin grafting seems to provide cosmetically acceptable results, while punch grafting tends to yield suboptimal cosmesis. Autologous cellular suspension transplants may be effective in repigmentation. All of the surgical techniques are operator dependent and vary from study to study. More studies are needed.
- There has been an increase in the number of RCTs seen in the literature in the field of vitiligo. However, standardization of definitions and assessment of treatment are needed to allow for ease of study comparison, in the future.

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Treatment of Hirsutism (Medical Interventions)

37

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INTRODUCTION

Hirsutism is a disorder in women in which there is excessive growth of terminal (coarse, medullated) hair within androgen-dependent areas such as the chin, upper lip, chest, breasts, abdomen, back, and anterior thighs. Hirsutism should be differentiated from hypertrichosis because the underlying etiologies and medical implications of these disorders are different. Hypertrichosis is an androgen-independent increase in hair growth that occurs in a generalized, nonsexual distribution. Hypertrichosis is most often caused by drug ingestion, although there are many other causes; while the causes of hirsutism are most often the result of increased quantity or activity of male sex hormones, or androgens, in the blood of afflicted female patients.

Women with hirsutism carry a significantly higher risk of developing psychological disorders.¹ In addition, hirsute women perceive themselves to be in poorer health than nonhirsute women, and there are fewer in employment despite having similar educational backgrounds.¹⁻³ In some women, the negative psychosocial implications are further compounded by additional cosmetically disturbing findings of androgen excess such as androgenetic (patterned) alopecia, acanthosis nigricans and acne. Dermatologists and, in recent years, nonphysician run cosmetic clinics are consulted to treat excess and unwanted hair. Given that the etiologies underlying hirsutism can be associated with medically important conditions such as infertility, insulin resistance, and diabetes, cardiovascular disease and endometrial carcinoma, appropriate medical evaluation of patients is essential.^{4,5}

EPIDEMIOLOGY

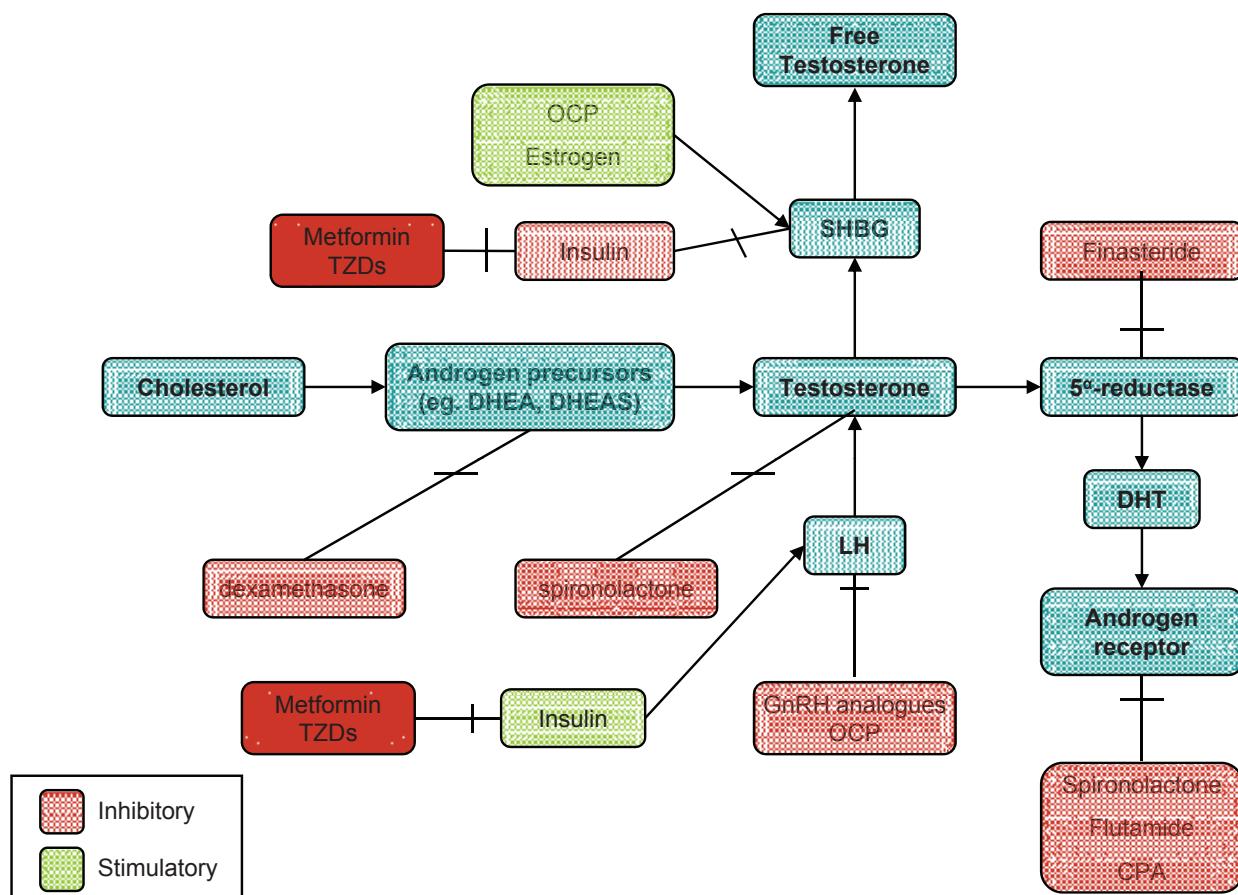
Hirsutism affects approximately 5-10% of reproductive age women.⁵⁻⁷ A 1993 marketing research survey of 25,000 women estimated that 41 million women in the United States had unwanted facial hair and that 22 million removed facial hair as frequently as once per week. (<http://sec.edgar-online.com/skinmedica-inc/s-1a-securities-registration-statement/2005/07/08/Section4.aspx>).

ETIOLOGY/DIAGNOSIS

Hirsutism, in the vast majority of cases, is a cutaneous manifestation of an underlying hormonal imbalance where androgens are in excess. It is also affected by increased sensitivity to androgens in the hair follicles, and the sebaceous glands around the hair follicles (target organ dysfunction).⁸ To be active in the skin, free (biologically active) testosterone (i.e., testosterone that is unbound to sex hormone binding globulin (SHBG)) must be converted to dihydrotestosterone (DHT) by the enzyme 5 α -reductase (Figure 37-1). Androgen sensitivity is partly determined by 5 α -reductase activity in the skin. Approximately 80% of women who exhibit increased serum androgens, namely testosterone, androstenedione and dehydroepiandrosterone-sulfate (DHEAS), manifest hirsutism.⁹ The most common cause of hirsutism is polycystic ovarian syndrome (PCOS) accounting for greater than 70% of cases.^{9,10} The next most common etiology is "idiopathic" hirsutism, which occurs in approximately 23% of hirsute patients who have regular menstrual cycles and do not have a detectable androgen excess by conventional testing.¹⁰ Other less common causes of androgen excess, resulting in hirsutism include nonclassic congenital adrenal hyperplasia (21-OH deficiency), the hyperandrogenic insulin-resistant acanthosis nigricans (HAIR-AN) syndrome, various endocrinopathies, androgen-secreting tumors, and androgenic drug intake.⁴

Briefly, diagnosis of hirsutism requires a thorough history and physical examination, with particular emphasis on the pattern and onset of hirsutism, menstrual irregularity, weight gain, and use of androgenic medications. The goals of evaluation are three-fold:

1. To determine the underlying etiology for the hirsutism (PCOS, endocrinopathies, androgenic medications, etc.).
2. To assess the amount, severity, and distribution of hirsutism as a baseline measure from which to benchmark response to therapy or progression.
3. To identify those patients at risk for associated medical problems (insulin resistance, cardiovascular disease, infertility, etc.).



Mechanism of action of the class of medications used to treat hirsutism

Drug	Mechanism of action
Oral contraceptive pills	1. Suppresses leutinizing hormone & ovarian androgen production 2. Increases sex hormone binding globulin
Antiandrogens	
Flutamide	Competitive inhibition of the androgen receptor
Finasteride	Inhibits 5α reductase
Spironolactone	1. Aldosterone antagonist 2. Competitive inhibition of the androgen receptor
Insulin sensitizers	
Metformin	Activates AMP-activated protein kinase thereby inhibiting hepatic gluconeogenesis
Thiazolidinediones	Bind peroxisome proliferator-activated receptors which decreases insulin resistance by sensitizing tissues to the action of insulin
Glucocorticoids	Suppresses adrenal androgens
Gonadotropin releasing hormone agonists	Suppresses ovarian steroidogenesis by decreasing levels of LH and FSH
Eflornithine topical cream	Inhibits ornithine decarboxylase and polyamine synthesis which is necessary for hair growth

FIGURE 37-1 Schematic of androgen biosynthesis and mechanisms of action of drugs used to treat hirsutism.

DHT-dihydrotestosterone, OCP-oral contraceptive pills, SHBG-sex hormone binding globulin, DHEA dehydroepiandrosteronesulphate, LH-luteinizing hormone, CPA-cyproterone acetate, TZDs-thiazolidinediones

The current standard for clinically grading hirsutism is by using the classic or modified Ferriman-Gallwey (FG) scale.¹¹ A score of 8 to 15 is compatible with mild hirsutism.^{12,13} Initial laboratory investigations may include total or free testosterone, DHEAS and 17-hydroxyprogesterone with further laboratory work-up and investigations guided by history and physical examination findings. There is some debate as to whether women with mild hirsutism (FG 8-15) require laboratory work-up. However, it is generally accepted that testing should be performed in all women with moderate to severe hirsutism (FG>15) or with hirsutism that is associated with menstrual irregularity, infertility, central obesity, rapid onset, acanthosis nigricans or clitoromegaly.¹⁴ Additional tests that could be considered based on clinical suspicion include a transvaginal ultrasound, CT/MRI of the abdomen and pelvis (for tumors), cranial MRI (for pituitary adenoma), prolactin, and dihydrotestosterone level, among other tests.

SEARCH METHODOLOGY

A MEDLINE search was performed between February and March 2010 using the search terms “hirsutism” and “treatment” to identify meta-analyses and randomized-controlled trials (RCT) that compared treatment options for hirsutism. Endocrinology and Obstetrics and Gynecology clinical groups’ guidelines and relevant bibliographies were also reviewed (Table 37-1).

TREATMENT OVERVIEW OF HIRSUTISM

Treatments used to manage hirsutism can be divided into two major categories: physical methods and pharmaceutical methods. Physical methods can be further broken down into temporary and permanent methods of hair removal. Temporary methods include shaving, waxing, plucking, and chemical depilatory agents. Bleaching can also be included in this category, although it is not truly a method of hair removal but only serves to lighten the hair.

Permanent methods of hair removal include photoepilation (laser treatment) and electrolysis.

Pharmaceutical management of hair removal can either be topical or systemic. Systemic treatments focus mainly on regulating androgen excess or peripheral androgen receptor function and, in women with PCOS or related syndromes with hyperinsulinemia, regulating insulin sensitivity. Common systemic treatments include oral contraceptive pills (OCPs), antiandrogens (spironolactone, flutamide, finasteride, and high dose cyproterone acetate [CPA]), insulin sensitizers (metformin and thiazolidinediones), gonadotropin-releasing agonists (e.g., nafarelin and leuprolide), and glucocorticoids (e.g., dexamethasone). Topical treatment includes eflornithine 13.9% cream, an ornithine decarboxylase inhibitor, and finasteride 0.25% cream (Table 37-2). Evidence from meta-analyses or, when they are unavailable, randomized-controlled trials comparing these different treatment modalities will be briefly described and discussed in the context of hair reduction in patients afflicted with hirsutism.

RESEARCH QUESTIONS AND ANSWERS

What is the comparative efficacy of OCPs versus placebo?

Oral contraceptive pills contain ethinyl estradiol (EE), a synthetic estrogen, in combination with a progestin. Estrogens increase hepatic production of SHBG, thereby reducing free testosterone concentration (the biologically active form of testosterone) (Figure 37-1). Most synthetic progestins are chemical derivatives of testosterone (known as 19-nortestosterone derivatives).¹⁵ First and second generation progestins consisting of norethindrone and progestins such as norethindrone acetate and ethynodiol diacetate that metabolize to norethindrone, and levonorgestrel and norgestrel have varying degrees of androgenic activity (Figure 37-2). Newer third generation progestins such as desogestrel and norgestimate possess minimal

TABLE 37-1—Key Meta-Analyses Examining Medical Treatment of Hirsutism

Authors	Year	Title
Martin KA, et al. (14)	2008	Evaluation and treatment of hirsutism in premenopausal women: an endocrine society clinical practice guideline
Van der Spuy, Z M, le Roux PA (16)	2003	Cyproterone acetate for hirsutism (Cochrane Database Systematic Review)
Swiglo BA, et al. (26)	2008	Clinical review: Antiandrogens for the treatment of hirsutism: a systematic review and meta-analyses of randomized-controlled trials
Brown J, et al. (28)	2009	Spironolactone versus placebo or in combination with steroids for hirsutism and/or acne (Cochrane Database Systematic Review)
Cosma M, et al. (44)	2008	Clinical review: Insulin sensitizers for the treatment of hirsutism: a systematic review and meta-analyses of randomized-controlled trials

TABLE 37-2—Adverse Effects of OCPs

Drug	Reported Doses	Main Adverse Effects		Pregnancy category
		Common	Serious	
Oral contraceptive pills (OCPs)	—	Gastrointestinal upset, breast tenderness, headache, cyclical weight gain, mood swings, lipid abnormalities (\downarrow HDL; \uparrow LDL)	Depression, VTE, myocardial infarction, stroke, pulmonary embolism	—
Spirostanolactone	50-200 mg/d	Irregular menses, breast tenderness, headaches, gastrointestinal upset, lethargy	Hyperkalemia Rare: hepatocellular toxicity, vasculitis, agranulocytosis	D
Finasteride	2.5-7.5 mg/d	Decreased libido, weakness, postural hypotension, dizziness	Rare severe myopathy, hypersensitivity reaction	X
Flutamide	125-500 mg/d	Galactorrhea, decreased libido, hot flashes, gastrointestinal upset, liver enzyme elevation, anemia, peripheral edema	hepatic failure, hypersensitivity, interstitial pneumonitis, leucopenia, thrombocytopenia	X
Metformin	1.5-1.7 g/d	Gastrointestinal upset, weakness, headache, decreased vitamin B12 levels, metallic taste	Lactic acidosis, pneumonitis, leukocytoclastic vasculitis	B
Thiazolidinediones	—	Edema, hypertension, headache, hypoglycemia, diarrhea	Increased risk of cardiovascular events, anemia, exacerbation of heart failure, fractures, arthralgias	C
Dexamethasone	0.5 mg qhs	Weight gain, hypokalemia, decreased bone density, immune suppression, depression	HPA axis suppression, fractures	C
Leuprorelin	3.75 mg IM monthly	Edema, headache, pain, depression, menopausal symptoms (hot flashes, decreased libido, vaginitis), gastrointestinal upset, weakness	Increases cardiovascular disease risk, gastrointestinal hemorrhage, leucopenia, renal failure	X
Eflornithine cream	BID, at least 8 hrs apart	Acne, pseudofolliculitis barbae, skin irritation, headache	Pancytopenia (systemic use)	C

DHT-dihydrotestosterone; OCP-oral contraceptive pills; SHBG-sex hormone binding globulin; DHEA dehydroepiandrosteronesulphate; LH-luteinizing hormone; CPA-cyproterone acetate; TZDs-thiazolidinediones

androgenic properties, but may carry a higher risk of blood clots (Table 37-2). Cyproterone acetate (CPA) (available worldwide except in the US) and drospirenone function as androgen receptor antagonists but typically do not increase androgenicity because they are structurally unrelated to testosterone. CPA (2 mg) combined with EE (0.035 mg) is marketed as Diane-35® (Berlex, Inc.) in Canada and Dianette in the UK. The drug is Health Canada approved for treatment of androgen-sensitive skin conditions including hirsutism (<http://www.bayer.ca/files/DIANE-35-PM-ENG-02OCT2008-123244.pdf>). While it is not indicated as an OCP, it provides effective birth control and will be included under the umbrella of the OCP designation. OCPs suppress luteinizing hormone (LH) and increase SHBG, thereby reducing concentrations of bioavailable testosterone (Figure 37-1). They also reduce adrenal androgen secretion and block androgens from binding to their receptor.¹⁴ Therefore, OCPs reduce hirsutism by reducing the concentration of bioavailable androgens and inhibit androgens from mediating their biologic effects in the skin.

Two clinical trials have evaluated the efficacy of OCPs versus placebo or no treatment in hirsute women. The first of these, a placebo controlled trial, analyzed 20 women with PCOS who took 2 mg CPA+ EE 35 mcg.^{16A} (Saeed R, Akram J, Changezi HU, Saeed M. Treatment of hirsutism in polycystic ovarian syndrome with Diane, 50 mcg ethynodiol diacetate and 2 mg cyproterone acetate. Specialist (1993) 9:109–112) cited in: 16) While there was no objective assessment of hirsutism, there was a significant subjective improvement in hair growth, although the confidence limits were large (odds ratio (OR) 45; 95% confidence interval (CI) 2.01, 1006.8). (Saeed R, Akram J, Changezi HU, Saeed M. Treatment of hirsutism in polycystic ovarian syndrome with Diane, 50 mcg ethynodiol diacetate and 2 mg cyproterone acetate. Specialist (1993) 9:109–112) cited in: 16)¹⁶ The second clinical trial examined 45 women with either idiopathic hirsutism or PCOS and evaluated the effectiveness of 150 mcg desogestrel+ EE 30 or 50 mcg (16 patients) versus 2 mg CPA+EE 35 mcg (10 patients) versus no treatment (19 patients) over 2 years.¹⁷ At the end

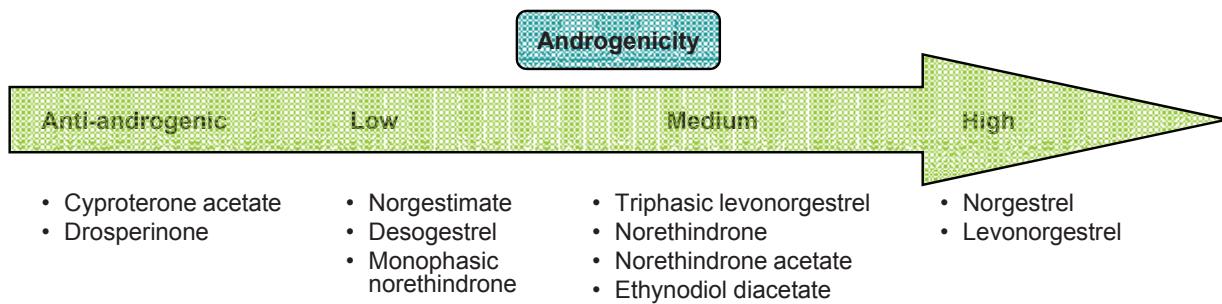


FIGURE 37-2 Schematic of androgenicity of various progestins.

of the two years, FG hirsutism scores were significantly reduced (-7.1 ± 0.6 ; $p<0.01$) in the women treated with OCPs.¹⁷ In a combined analysis of these two trials, pooled odds ratio demonstrated that there was a greater reduction in FG hirsutism scores with OCP therapy compared to placebo or no therapy (weighted mean difference (WMD) -8.0 , 95% CI, -11.0 to -4.5).¹⁴

Drosperinone (DRSP) is a novel 4th generation progestin derived from 17 α -spironolactone. It possesses antiandrogenic and antimineralcorticoid activity similar to that of spironolactone.^{18,19} Four studies enrolling between 18 to 52 women with PCOS or mixed etiology hirsutism found a decline in FG scores with 3 mg DRSP+EE 30 mcg (Yasmin®, Bayer HealthCare Pharmaceuticals) treatment over 6 to 12 months of treatment (Table 37-3).¹⁸⁻²¹ All studies lacked a control group, thereby making it difficult to accurately assess the clinical relevance of the findings. In all of the studies, testosterone levels improved significantly and there was a dramatic rise in SHBG. There were no significant adverse events and the drug was well tolerated. A positive overall profile of action with respect to body weight and blood pressure was observed and was attributed to drosperinone's anti-mineralocorticoid activity.²¹

A comparative randomized study between DRSP+EE and CPA+EE combinations in 91 women found equivalent efficacies between the two OCPs (Table 37-3).²²

Based on these limited studies, monotherapy with OCPs reduces hirsutism in women afflicted with PCOS or idiopathic hirsutism compared to placebo. The studies reviewed used either OCPs with an antiandrogenic progestin, or a third generation progestin with minimal androgenic properties. Aside from one head- to-head study of DRSP+EE and CPA+EE, there are no other head-to-head comparisons of other classes of progestins. Recent clinical guidelines recommend the use of OCPs as a first line treatment of hirsutism in women who do not wish to conceive.¹⁴

Although widely prescribed and typically well tolerated, OCPs do have several adverse effects (Table 37-2). Among these is the concern for venous thromboembolism (VTE), which is elevated with all OCPs, as a class but may be higher with certain types of progestins. A Danish national cohort study that included 10.4 million woman years of observation, found that the risk for VTE in women who took combined OCPs decreased with longer duration of use and with decreasing dosage of estrogen. For the same dose of estrogen and duration of use, OCPs containing

TABLE 37-3—Uncontrolled Clinical Trials of DRSP/EE

Study	Sample	Treatment duration	Result
Drosperinone + ethinyl estradiol alone (no control group)			
Pehlivanov <i>et al.</i> 2007 (19)	20 ♀ with PCOS	6 cycles	23% drop in FG score. Mean difference in FG score compared to baseline: -2.55 (95% CI -4.59 to -0.50 ; $p=0.0159$)
Guido <i>et al.</i> 2004 (21)	18 ♀ with PCOS	12 cycles	16% drop in FG score. (16.20 ± 5.81 at baseline; 13.53 ± 4.96 at 12 months ($p<0.01$))
Gregoriou <i>et al.</i> 2008 (20)	52 ♀	12 months	FG score reduced to 51.8% of baseline
Batukan <i>et al.</i> 2006 (18)	50 ♀ with mod-severe hirsutism	12 months	Mean FG score declined by 78%
Drosperinone + ethinyl estradiol versus Cyproterone acetate + ethinyl estradiol			
Batukan <i>et al.</i> 2007 (22)	91 ♀ (48 DRSP/43 CPA)	12 months	No significant difference between groups in % reduction of total FG score (0.80 (0-0.42) vs 0.81 (0-0.75)) respectively ($p=0.6$)

FG=Ferriman-Gallwey score; DRSP=drosperinone; CPA=cyproterone acetate; PCOS=polycystic ovarian syndrome

cyproterone, desogestrel, gestodene, or drospirenone were associated with a higher risk of VTE (approximately 2-fold higher risk) than pills containing levonorgestrel (LNG).²³ This finding was refuted by a more recent study, which confirmed the elevated risk of VTE with OCPs as a class, but found no significant elevation of risk among those using DRSP + EE versus other low-dose COCs (including LNG + EE (crude OR for DRSP + EE versus low-dose LNG/EE was 1.0 (95% CI 0.6-1.6), and the adjusted OR was 1.0 (95% CI 0.6-1.8). Practically speaking, even with a 2-fold higher risk with some OCPs, the overall risk remains low since the absolute risk of VTE with any use of combined OCPs is less than one in 1000 woman years.²³ Where OCP therapy is contemplated, women should be evaluated for risk factors for VTE which includes a personal or family history of VTE, increased body mass index, and smoking.

What We Know

- OCP therapy is associated with a significant reduction in hirsutism scores compared to placebo or no treatment. Recent guidelines recommend OCPs as the first line therapy for hirsutism, given the teratogenic potential for antiandrogens
- OCPs should be chosen with a progestin component of low androgenicity or with antiandrogenic effects.
- Desogestrel, CPA, and DRSP containing OCPs are the best studied.

What is the comparative efficacy of antiandrogens versus placebo?

Spironolactone

Spironolactone is an aldosterone antagonist with structural similarity to progestins. The drug is a competitive inhibitor of the androgen receptor and also inhibits androgen biosynthesis and increases androgen metabolism (Figure 37-1).²⁴ There are two RCTs that have compared spironolactone to placebo for the treatment of hirsutism. One RCT by McClellan et al. compared 38 women to "idiopathic" hirsutism (baseline FG score not reported) taking spironolactone 100 mg daily (n=19) to women taking a placebo (n=19).²⁵ After 9 months, the women taking spironolactone demonstrated a trend towards subjective improvement, but this did not achieve statistical significance. The objective outcome measure (change in hair shaft diameter of a sample of hair taken from the thigh), was not significantly improved by spironolactone. Furthermore, only 58% (11/19) of patients completed the treatment arm. A more recent meta-analysis utilizing a Hedges' g approach to calculate a standardized mean difference from the aforementioned study, found that this subjective improvement was statistically different between the hirsute women taking spironolactone and the women taking placebo

(standardized mean difference (SMD) -1.1, 95% CI -2.1, -0.05).^{25,26}

A second RCT by Moghetti et al. compared 40 hirsute women taking antiandrogens spironolactone, flutamide, or finasteride to placebo (n=10 in each group) for a period of 6 months.²⁷ Objective outcome measures were reduction in hair shaft diameter and FG score. In the group taking spironolactone versus placebo, there was a significant decrease in hair diameter ($p<0.01$) and in FG score ($p<0.001$). Although the actual study did not provide statistical analysis of patient self-evaluation of clinical outcome, a meta-analysis found significantly improved subjective hirsutism scores compared to the women taking placebo (mean weighted difference in favor of treatment (MWD) -7.2, 95% CI -10.98, -3.42).²⁸ Furthermore, two separate meta-analyses combining these two trials demonstrated a subjective improvement in hair growth in patients taking 100 mg/d spironolactone compared to placebo (OR 7.18, 95% CI 1.96, 26.28).^{25,27,28} (WMD -4.8 (-7.4, -2.2); I²=0%)²⁶ (Figure 37-3) Adverse effects of spironolactone included a dose-dependent association with menstrual irregularity, hyperkalemia and increased diuresis with associated postural hypotension and dizziness (Table 37-2).

The FDA package insert for spironolactone states that spironolactone at dosages several times higher than those used in humans, resulted in mammary tumors in rats (http://www.accessdata.fda.gov/drugsatfda_docs/label/2008). Although no significant causal association with breast cancer have been found in women exposed to spironolactone, it is recommended either to exercise caution or not to give spironolactone to women with a genetic predisposition to breast cancer or other estrogen-dependent malignancies.²⁹ As with all antiandrogens, spironolactone is a teratogen that can cause pseudohermaphroditism in male fetuses. Adequate contraception is therefore a requirement with therapy.

Finasteride

Finasteride is an inhibitor of type II 5a-reductase (Figure 37-1). A meta-analysis of three RCTs analyzing patients with PCOS or idiopathic hirsutism being treated with 5-7.5 mg finasteride exhibited a significant reduction in FG scores after 6 months of treatment compared to placebo (WMD -2.9; 95% CI -5.3, -0.6) (Figure 37-3).^{26,27,30,31} A reduction in dihydrotestosterone level was also seen in finasteride-treated patients. While the aforementioned studies used higher dosages of finasteride, another randomized trial (n=56 hirsute patients with either PCOS or idiopathic hirsutism) demonstrated that dosages of 2.5 mg and 5 mg daily of finasteride resulted in significant reductions in modified FG scores ($p<0.001$), and that there were no significant differences between the two dose groups after 12 months of treatment.³² Although the study lacked a control group, the findings suggest that dosages ranging from 2.5-7.5 mg may be similarly efficacious to treat

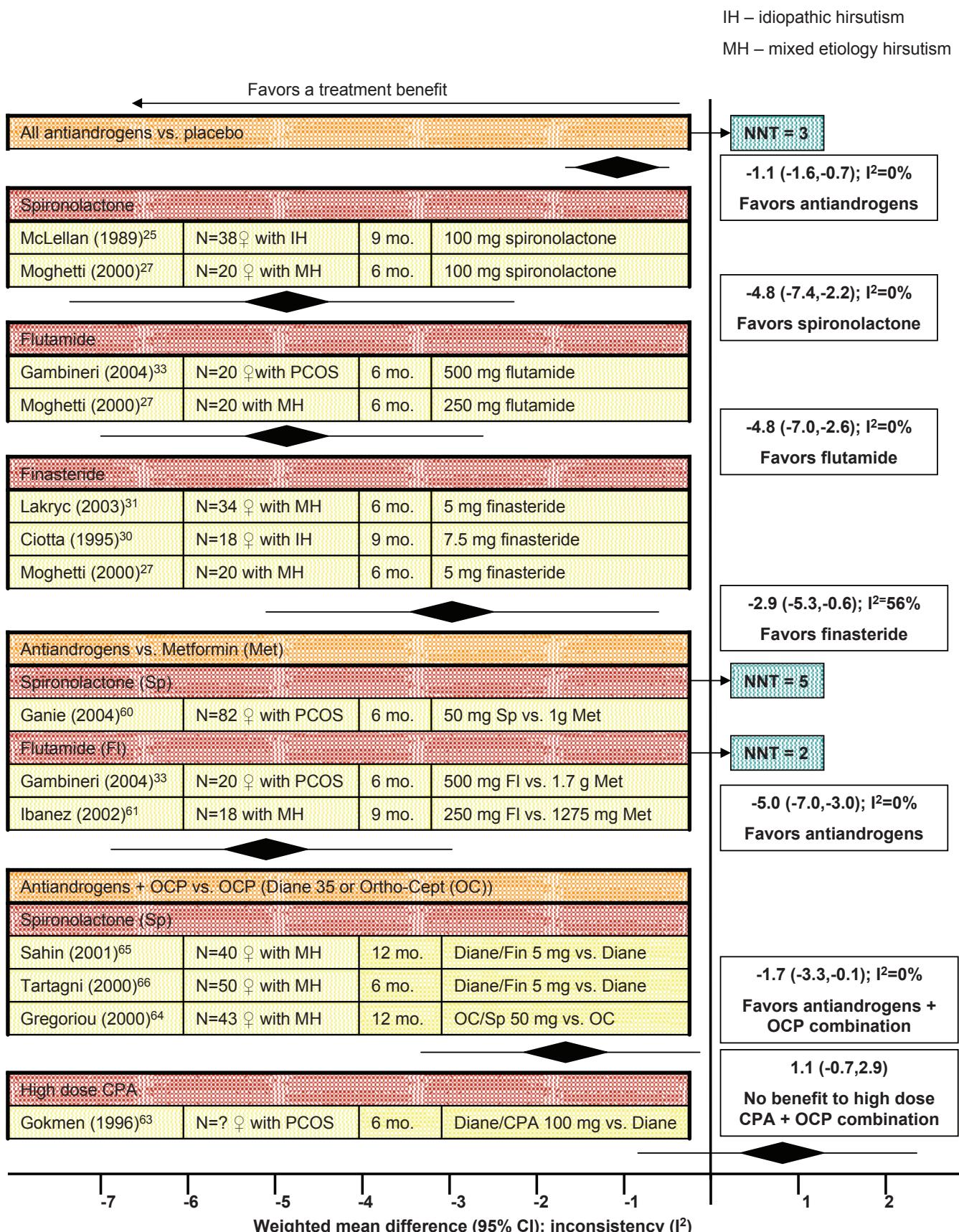


FIGURE 37-3 Summary of antiandrogens for the treatment of hirsutism. (Adapted from Swiglo BA, et al. *J Clin Endocrinol Metab*. 2008;93(4):1153–60.)

DHT-dihydrotestosterone; OCP-oral contraceptive pills; SHBG-sex hormone binding globulin; DHEA dehydroepiandrosteronesulphate; LH-luteinizing hormone; CPA-cyproterone acetate; TZDs-thiazolidinediones

hirsutism. While finasteride was well-tolerated in the trials above, adverse effects can include decreased libido, hypersensitivity, postural hypotension, dizziness, and rarely severe myopathy (Table 37-2). Like other antiandrogens, finasteride is pregnancy category X because of its teratogenic potential to induce pseudohermaphroditism in the male fetus. Therefore, a reliable method of contraception is required in women with child-bearing potential who take this drug.

Flutamide

Flutamide is a pure nonsteroidal antiandrogen that displays a dose-response inhibition of the androgen receptor (Figure 37-1). In general, treatment does not alter serum androgens or other hormone levels. Doses of 250-750 mg/d have shown efficacy in reducing hirsutism. A meta-analysis of two RCT comparing patients taking 250-500 mg flutamide to patients taking a placebo, calculated a significant improvement in hirsutism, in the context of lower FG scores, after 6 months of treatment (WMD -4.8; 95%CI -7.0, -2.6) (Figure 37-3).^{26,27,33} The lower 250 mg dose is preferred because of better patient tolerability and fewer adverse effects. Patient drop-out rates are high in virtually all studies examining flutamide, particularly in those groups receiving >250 mg daily.^{34,35} A RCT examining 125 mg, 250 mg, and 375 mg daily doses of flutamide + OCP (with levonorgestrel) versus placebo + OCP found that all dosages resulted in a significant decline in hirsutism score after 12 months ($p=0.02$), but there were no significant differences among the 3 dosages of flutamide.³⁶ Other small studies lacking a control group have shown efficacy of 62.5 and 125 mg daily doses.^{37,38} Based on the limited evidence provided, low dose flutamide (125 mg daily) may be equally efficacious to higher dose regimens.³⁶ Like other antiandrogens, flutamide is a teratogen and requires concomitant use of contraception in fertile women. The most serious adverse effect of flutamide is fatal and nonfatal hepatotoxicity which is dose dependent and occurs in fewer than 1% of patients (it commonly occurs within the first 3 months of treatment) (Table 37-2).^{39,40} Overall, the clinical utility of flutamide is constrained by this risk of hepatotoxicity.

A more recent comparative study examined 44 unselected hirsute women taking combination of flutamide 125 mg and finasteride 5 mg with patients taking either antiandrogen alone.⁴¹ The study found that combination therapy reduced FG scores to a similar extent as flutamide alone (49% vs. 45% decrease in scores, $p>0.05$). However, combination therapy resulted in significantly greater improvement in hirsutism scores, compared to finasteride alone (49% vs. 32%, $p<0.05$) after 12 months of treatment. Similarly, other randomized-controlled trials comparing finasteride and flutamide directly demonstrate that flutamide is superior to finasteride in reducing hirsutism.^{42,43}

Based on these studies, flutamide alone is as effective as combination therapy (flutamide and finasteride), and is superior to finasteride as a single agent in reducing hirsutism. The limiting factor for flutamide remains the risk of hepatotoxicity.

ANTIANDROGENS AS A CLASS

To answer whether antiandrogens as a class of drugs can ameliorate hirsutism, the above meta-analysis by Swiglo et al. incorporated five RCTs comparing patients taking antiandrogens to patients taking placebo and found that women treated with antiandrogens had significantly lower hirsutism FG scores than the placebo group (sample mean difference (SMD) -3.9; 95% CI -5.4, -2.3) (Figure 39-3).^{25-27,30,31,33} The antiandrogens included in this meta-analysis were spironolactone, finasteride, and flutamide. Subgroup analysis demonstrated negligible differences between the efficacies of the three antiandrogens when compared to each other. Another study not included in this meta-analysis suggested that patients treated with spironolactone maintained lower hirsutism scores for a significantly longer period after cessation of therapy (at least 1 year), as compared to patients taking finasteride.⁴⁴ However, the meta-analysis did not directly address durability of treatment responses. A significant limitation of all studies in the field was a paucity of RCTs reporting patient self-assessment of hirsutism as an outcome measure of treatment efficacy.

The majority of the RCTs from which conclusions were drawn had small sample sizes and methodologic shortcomings (i.e., no blinding). Thus, the overall quality of evidence supporting antiandrogen use for the treatment of hirsutism is low. In conclusion, there is weak but positive evidence demonstrating that antiandrogens as a class improve hirsutism in women with PCOS and idiopathic hirsutism. Based on the meta-analysis, three women would need to be treated for one to notice an improvement in her hirsutism (NNT). Overall, flutamide may be more effective than finasteride, although the meta-analysis did not bear

What We Know

- Antiandrogens are an effective treatment for hirsutism (3 women need to be treated with spironolactone, flutamide or finasteride (NNT) for one to notice an improvement).²⁶
- Treatment with antiandrogens needs to be continued for at least 6 months to see a benefit.
- Flutamide may be more effective than finasteride but its risk of fatal and nonfatal hepatotoxicity limits its clinical utility compared to other antiandrogens.
- Antiandrogens can feminize a male fetus and must be used in conjunction with adequate contraception

out this difference. In addition, spironolactone may result in a longer period of reduced hair growth compared to finasteride although more studies are needed to confirm this conclusion. Ultimately, the decision to select a particular antiandrogen depends upon patient preferences and tolerability.

Are antiandrogens or OCPs more efficacious for the treatment of hirsutism?

A Turkish study compared hirsutism scores in 42 women taking CPA (2 mg)-EE (35 mcg) combination (Diane 35) to patients taking 5 mg/d finasteride over 9 months. (Saeed R, Akram J, Changezi HU, Saeed M. Treatment of hirsutism in polycystic ovarian syndrome with Diane, 50 mcg ethinyl estradiol and 2 mg cyproterone acetate. Specialist (1993) 9:109–112) cited in: 16) While both treatments reduced hirsutism scores compared to baseline scores, there was no significant difference between the finasteride and OCP group (WMD -2.5; 95% CI, -5.4 to 0.4) based on meta-analysis.^{14,45} Another study examining 40 women taking CPA (25 mg/d) and EE (20 mcg/d) to patients taking 5 mg/d finasteride for 9 months also found no significant differences in hirsutism scores between the groups at the end of the study period.⁴⁶ An additional two studies comparing patients taking flutamide 250 mg/d alone with patients taking spironolactone 100mg/d plus Diane-35, concluded that there were similar F-G scores at the end of the study period (6 months and 9 months, respectively).^{47,48} In conclusion, CPA+EE and finasteride at the dosages studied are equally efficacious with regard to ameliorating hirsutism. Also, the addition of spironolactone to Diane-35 did not confer an additional benefit in reducing hirsutism as compared to patients taking flutamide alone. Unfortunately, there were no comparative studies examining OCPs available in the United States and other antiandrogens.

In hirsute patients with PCOS, can monotherapy with insulin sensitizing drugs reduce hirsutism?

Hyperinsulinemia can cause hyperandrogenemia in two ways: (a) insulin can bind to insulin-like growth factor-1 (IGF-1) receptor and, thereby, mimic the action of IGF-1, which augments androgen production by the theca cell in response to LH; (b) insulin decreases SHBG production, resulting in increased levels of circulating free testosterone (Figure 37-1).⁴⁹ Metformin and thiazolidinediones (TZDs) are the two main classes of drugs that have been studied with regard to their effect on hirsutism. Metformin reduces androgen production by inhibiting glucose output, thereby, effectively lowering insulin levels. TZDs, such as pioglitazone and rosiglitazone, sensitize tissues to insulin in the liver, skeletal muscle and adipose tissue.

Metformin

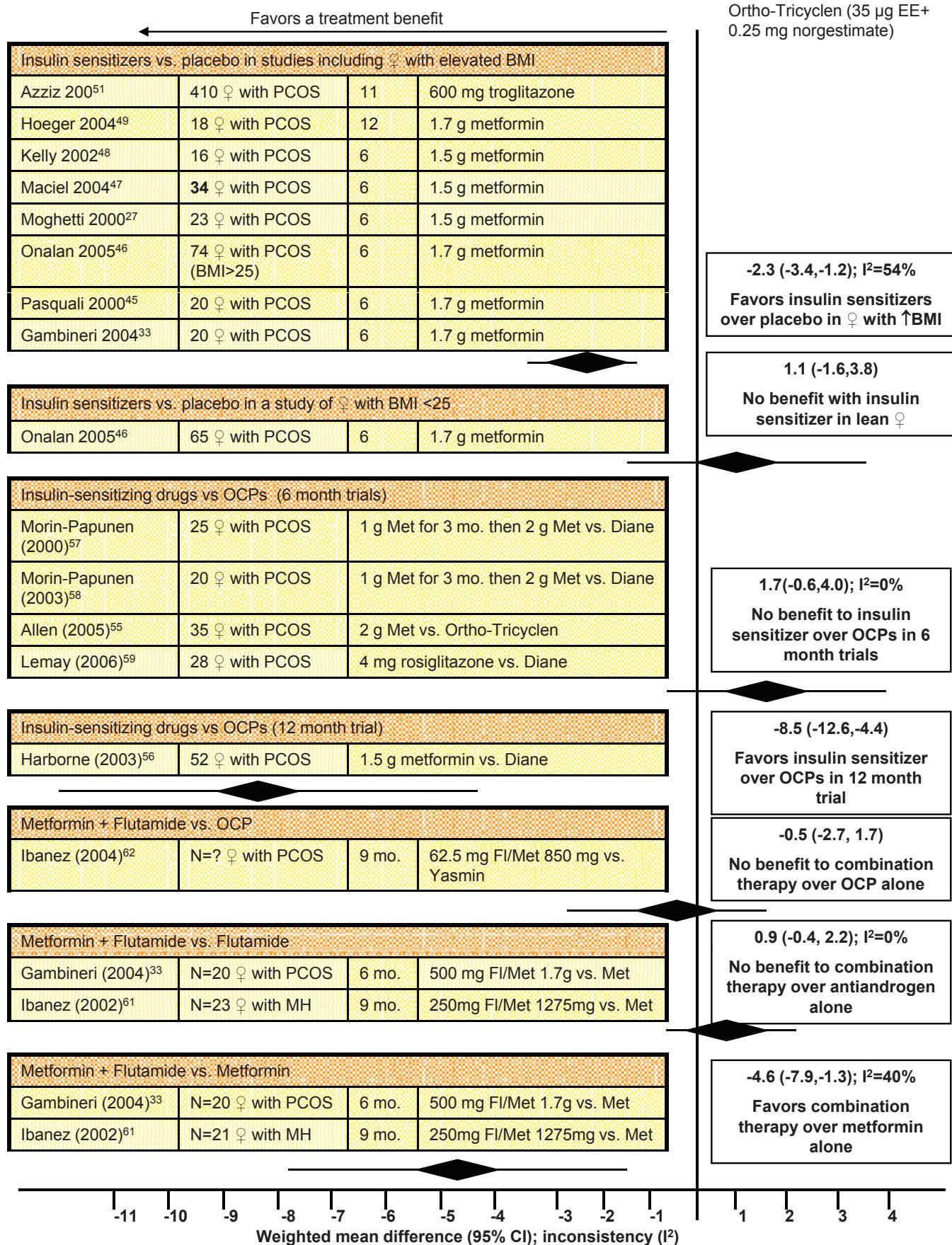
A meta-analysis of all trials examining insulin sensitizers identified seven RCTs that examined the effectiveness of metformin in lowering Ferriman-Gallwey scores of women with PCOS over 6-12 months of treatment compared to placebo (Figure 37-4).^{27,33,50–55} The authors determined the pooled weighted mean difference (WMD) between treatment and control interventions and the associated 95% confidence interval. They also calculated inconsistency (I^2), which describes the quantity of variance across trials not caused by chance, where $I^2 < 25\%$ corresponds to less inconsistency and $I^2 > 75\%$ corresponds to large inconsistency. For the meta-analysis, the authors subdivided one trial (Onalan study) into two separate studies.⁵² In this study, patients were randomized according to BMI (lean vs. obese) and the two subgroups were analyzed separately for a total of “8” studies examining metformin versus placebo. Sample sizes ranged from 16 to 74 women and the dose of metformin used ranged from 1.5-1.7 g/day. Two of the “8” trials showed significantly decreased FG scores in the metformin-treated women compared to placebo;^{52,56} while, the remaining 6 trials showed no difference.^{33,51,53–55} Meta-analysis of all “8” trials together found no significant beneficial effect of metformin on FG scores compared to placebo (WMD –1.4; 95% CI –2.8, 0.1).⁵⁰ The overall quality of the RCTs on which the meta-analysis is based is low to very low. Based on this evidence, metformin does not significantly reduce hirsutism scores when compared to placebo in patients with PCOS.

Obese Versus Lean Patients with PCOS

Interestingly, subgroup analysis of the study that stratified women according to BMI found a significant beneficial effect for metformin compared with placebo in obese women with PCOS (WMD –2.5, 95% CI –3.5, –1.5), but not in their lean counterparts (WMD 1.1; 95% CI –1.6, 3.8) (Figure 37-4).^{50,52} The random effects pooled estimate of all studies that enrolled either overweight or obese women (i.e., $BMI > 2SD$ above 25 kg/m^2) or a mixed population of lean and obese women also showed significant reduction in FG score (–2.3, 95% CI –3.4, –1.2).^{33,50–55} Although there was only one study that analyzed only lean women,⁵² the evidence suggests that reducing hirsutism with insulin-sensitizing drugs may be more efficacious in obese patients. Nevertheless, larger randomized-controlled studies to verify these findings are necessary.

Thiazolidinediones

There was only one RCT examining TZDs versus placebo (Figure 37-4). The study included premenopausal women with PCOS (n=410). Treatment with 600 mg daily of troglitazone (a drug that is no longer available) was better than placebo at lowering FG scores (WMD –2.4; 95% CI –3.8, –1.0).^{50,57} Adverse effects were similar between treatment

**FIGURE 37-4** Summary of antiandrogens for the treatment of hirsutism.

DHT-dihydrotestosterone; OCP-oral contraceptive pills; SHBG-sex hormone binding globulin; DHEA dehydroepiandrosteronesulphate; LH-luteinizing hormone; CPA-cyproterone acetate; TZDs-thiazolidinediones

and control groups with the most common adverse event being elevations of transaminase levels. The safety of TZDs has recently come into question with reports of increased cardiovascular events, heart failure, macular edema, and osteoporotic bone fractures (particularly in post-menopausal women) in otherwise normal women with glucose intolerance.^{58–60} These adverse effects may limit patient acceptability and utility of this class of drugs.

One study compared hirsute patients taking rosiglitazone (4 mg/d) to patients taking metformin (850 mg twice daily) (n=96 pts) for 24 weeks. At the end of the study period, the patients taking rosiglitazone had significantly greater reductions in F-G scores (40% reduction) as compared to the patients taking metformin (19% reduction).⁶¹ While rosiglitazone was well tolerated in the study, the adverse effects of rosiglitazone dampen its therapeutic efficacy.

Insulin Sensitizers as a Class

A meta-analysis of all the placebo-controlled comparisons of insulin-lowering drugs as a class for the treatment of hirsutism shows a small but significant benefit (WMD –1.5; 95% CI –2.8, –0.2).⁵⁰ However, the quality of evidence on which this conclusion is based is low to very low and there was significant inconsistency between trials ($I^2 > 75\%$).⁵⁰

What is the efficacy of insulin-lowering drugs compared to other hirsutism treatments?

Insulin-Lowering Drugs Versus OCPs

A meta-analysis was performed of five trials comparing insulin-lowering drugs (4 RCTs using metformin 1–2 g^{62–65}, 1 RCT using rosiglitazone 4 mg⁶⁶) to OCPs (4 trials used Diane-35 (2 mg CPA + 35 mcg EE)^{63–66} and 1 trial used 35 mg EE + 0.25 mg norgestimate⁶² (Ortho-Tricyclen® Ortho-McNeil-Janssen Pharmaceuticals, Inc.) (Figure 37-4). The trials enrolled between 20–52 women with PCOS and treatment duration varied between 6–12 months. The analysis found no significant difference in hirsutism scores between the treatments (WMD –0.5; 95% CI –5.0, 3.9), but there was large inconsistency across studies ($I^2 = 79\%$).^{50,62,64–66} However, subgroup analysis showed that therapy with metformin for 12 months significantly reduced FG scores compared to patients taking Diane-35 or OCPs for 12 months (WMD –8.5; CI 95% –12.6, –4.4) (Figure 37-4).^{50,63} Whereas for most antiandrogens, treatment benefit is significant at 6 months, a longer duration of therapy may be required to see improved hirsutism scores in patients taking insulin lowering therapy.

Insulin-Lowering Drugs Versus Antiandrogens

A total of three RCTs were identified by Cosma et al. as being suitable for inclusion in their meta-analysis of insulin

sensitizers versus antiandrogens (Figure 37-3).^{33,50,67,68} The trials included 18–82 women with PCOS or mixed etiology of hirsutism. All three trials compared metformin (dose ranges from 1 g to 1.7 g) to either spironolactone 50 mg (1 trial), or flutamide 250 mg, or 500 mg (2 trials). The meta-analysis demonstrated that patients treated with antiandrogens had significantly lower hirsutism scores compared to patients taking metformin (WMD –3.7; 95% CI –6.8, –0.6).^{33,50,67,69} In addition, those patients taking flutamide benefited more (WMD –5.0; 95% CI –7.0, –3.0) (NNT=2) than those patients taking spironolactone (WMD –1.3; 95% CI, –2.6, –0.03) (NNT=5).⁵⁰ Follow-up was 6 to 9 months and because other trials have shown better responses with metformin at 12 months of treatment, the full benefit of metformin may not have been realized in these studies. Nevertheless, based on these studies, hirsute women with PCOS treated with antiandrogens, will have a significantly better treatment response compared to those taking metformin.

Combination Systemic Therapy and their Effects on Hirsutism

Does the addition of antiandrogens to OCPs more significantly benefit hirsutism compared with OCPs alone?

Swiglo et al. performed a meta-analysis on four RCTs of women treated with antiandrogens and OCPs versus OCPs alone (Figure 37-3). The four clinical trials enrolled 20 to 43 women with PCOS, IH, or mixed etiology hirsutism.^{26,70–73} Baseline FG scores were comparable between treatment groups. Antiandrogens studied included 5 mg finasteride (2 trials),^{72,73} 50 mg spironolactone (1 trial),⁷¹ and 100 mg CPA (1 trial).⁷⁰ Three trials used Diane-35 (0.035 mg EE + 2 mg CPA)^{70,72,73} and 1 trial used 0.030 mg EE + 0.150 mg desogestrel (Ortho-Cept® Jannsen-Ortho, Inc.),⁷¹ and treatment ranged from 6–12 months. Meta-analysis of all four trials showed no significant difference between treatment groups (WMD –0.8; 95%CI –2.3, 0.7).^{26,70–73} Subgroup analysis of the antiandrogens, however, did favor treatment with finasteride or spironolactone combined with OCP over OCP alone (WMD –1.7; 95% CI –3.3, –0.1) (NNT=6).^{26,71–73} Based on these studies, combination therapy with spironolactone or finasteride plus an OCP may confer additional benefit over OCPs alone for reducing hirsutism.

Does the addition of metformin enhance an antiandrogen's effect on reducing hirsutism compared to monotherapy with either an antiandrogen, OCP, or metformin alone?

A meta-analysis of two trials compared treatment to 1.275–1.7 g metformin combined with flutamide versus flutamide

alone for 6 and 9 months (flutamide dose 250 – 500 mg) (Figure 37-4). The meta-analysis did not find a significant added benefit from metformin compared to flutamide alone (WMD 0.9; 95% CI –0.4, 2.2).^{26,33,68} Thus, flutamide is sufficient to reduce hirsutism and the addition of metformin confers no additional benefit. It is uncertain whether a longer duration of treatment (i.e., 12 months) or stratification for subjects with elevated BMI would have shown a greater benefit in the metformin add-on group.

Combination therapy of metformin plus flutamide did not show added treatment benefit over OCP alone (WMD –0.5 (–2.7, 1.7) (Figure 37-4).^{26,33,68}

Two trials examining combination therapy of metformin and flutamide versus metformin monotherapy both showed a treatment benefit with combination therapy over metformin alone (WMD of these two studies –4.6 (–7.9, –1.3); I²=40%; NNT=2) (Figure 37-4).^{26,33,68}

In women with hyperandrogenism, do glucocorticoids improve hirsutism?

In the setting of classic CAH caused by 21-hydroxylase deficiency, long-term glucocorticoids suppress adrenal androgens and are effective in managing hirsutism as well as in normalizing ovulatory cycles. In women with NCAH, glucocorticoids at low doses reduce adrenal androgens, but are typically used in reproductive age women to induce ovulation, thereby improving infertility. A minority of hyperandrogenic women, including some with PCOS, who have functional adrenal hyperandrogenism, may also be glucocorticoid sensitive. A few small trials have examined whether glucocorticoids improve hirsutism.

What We Know

- Antiandrogens are more effective than metformin (NNT =2 for flutamide vs. metformin; NNT=5 for spironolactone vs. metformin)²⁶
- The addition of antiandrogens (spironolactone or finasteride) to OCPs is more efficacious than OCPs alone (NNT=6)²⁶
- The addition of an antiandrogen (flutamide) to metformin is more efficacious than treatment with metformin alone (NNT=2)²⁶
- Weak evidence shows limited to no significant beneficial effect of insulin sensitizers (metformin and TZDs) as a class for hirsutism.
- Although pooled studies of metformin show no beneficial effect on hirsutism scores, metformin may be beneficial in reducing hirsutism in overweight and obese patients with PCOS, especially those patients who have taken metformin for at least 12 months.

A trial of 30 women with NCAH comparing hydrocortisone 10 mg bid (n=16), versus CPA 50 mg daily from the 5th to the 25th day of the menstrual cycle, combined with estradiol 3 mg daily over the last 10 days of CPA administration (n=14), found a 54% reduction in FG score after 1 year of treatment in the CPA group, but only a slight decrease (26%) with hydrocortisone treatment. By contrast, androgen levels dropped significantly in the hydrocortisone group but not among subjects taking CPA.⁷⁴ This interesting finding emphasizes the importance of peripheral androgen receptors in the clinical expression of hyperandrogenism. A German study found similar results.

A randomized trial of 25 unselected women with hyperandrogenemia and hirsutism and without demonstrated adrenal hyperandrogenism found no statistically significant difference between groups treated with dexamethasone and spironolactone (n= 15) versus spironolactone (n=10) monotherapy over 6 months.⁷⁵

In women with glucocorticoid-sensitive hyperandrogenic hirsutism not related to NCAH, a controlled trial comparing dexamethasone treatment to spironolactone (n=54 hirsute women randomized to take spironolactone 100 mg/day, dexamethasone 0.37 mg/day, or both dexamethasone and spironolactone), showed a significant decrease in FG scores after 1 year in all groups. The reduction in hirsutism score was greater when spironolactone was included in the treatment regimen compared to dexamethasone alone (p<0.05).⁷⁶ Androgen levels decreased significantly only in the dexamethasone and dexamethasone plus spironolactone-treated groups. Interestingly, dexamethasone provided a prolonged remission of hirsutism at 1 year post-therapy; while hirsutism scores returned to baseline at 1 year after withdrawal of therapy in those who received spironolactone alone.⁷⁶ Although glucocorticoids modestly reduced hirsutism in hyperandrogenic women, the adverse effects, including adrenal atrophy, hypertension, weight gain, striae, and decreased bone mineral density preclude their regular use in hirsute women with the exception of those with classic CAH and those women with NCAH requiring treatment for infertility.

Are GnRH analogs effective in reducing hirsutism in hyperandrogenic women?

Chronic GnRH therapy suppresses LH and to a lesser extent FSH, leading to reduced ovarian androgen production. Since hirsutism is partially caused by functional gonadotropin hyperandrogenism, GnRH therapy should lead to reduced hirsutism scores. Indeed, uncontrolled trials have demonstrated mild reductions in FG scores compared to baseline in hyperandrogenic women treated with a GnRH agonist.^{77,78} In a RCT that compared nafarelin alone, an OCP (EE plus norethindrone) alone or OCP plus nafarelin combination therapy, there was a significant reduction in hair shaft diameter in the patients

TABLE 37-4—Summary of Trials Analyzing Gonadotropin-Releasing Hormone (GnRH) Agonists in the Treatment of Hirsutism

Drug comparison	Dose Range	Follow-up	Summary of studies
<i>GnRH vs. OCPs</i>			
Heiner et al. 1995 (72)	400 µg nararelin vs. 1 mg norethindrone+ 35 µg EE vs. 400 µg nararelin+ 1 mg norethindrone+ 35 µg EE	24 wks	Significant decrease in hair shaft diameter only in the combination therapy group
Carre et al. 1995 (73)	3.75 mg decapeptyl q4 wks × 24 wks vs. 1 mg norethindrone+ 35 µg EE cyclically vs. 3.75 mg decapeptyl q4 wks × 24 wks + 1 mg norethindrone+ 35 µg EE cyclically	24 wks	Similar decreases in FG scores across all treatment groups
<i>GnRH +/- OCPs versus antiandrogens</i>			
Bayhan et al. 2000 (74)	3.75 mg leuprolide vs. 5 mg finasteride	6 mo	The mean % change (+/- SD %) in FG scores: GnRH: 36% (+/- 14%) Finasteride: 14% (+/- 11%)
Carmina et al. 1997 (75)	3.75 mg decapeptyl + 0.625mg EE+ 10 mg medroxyprogesterone acetate vs. CPA 50 mg+ 50 µg EE	1 yr	FG scores decreased in both groups but remained low after 1 year of further follow-up in the patients receiving decapeptyl

taking the OCP plus naftarelin after 24 weeks of treatment compared to the other two treatment arms (Table 37-4).⁷⁹ While the RCT showed a beneficial effect of combination therapy, other trials concluded that GnRH agonists added to OCPs did not further reduce FG scores or hair diameter when compared with OCP alone (Table 37-4).⁸⁰⁻⁸²

A comparative study (n=60 women with idiopathic hirsutism) examined GnRH alone (depot leuprolide 3.75 mg) versus 5 mg finasteride. FG scores were decreased more in women treated with leuprolide compared to women taking finasteride (Table 37-4).⁸³ When comparing high-dose CPA (50 mg) plus ethinyl estradiol with GnRH agonist therapy (Decapeptyl 3.75 mg), there was a similar decrease in mFG scores at 1 year in both groups; however, the reduction in hirsutism was sustained for a longer period of time in the GnRH agonist group, with hair growth remaining significantly decreased 1 year after withdrawal of therapy (Table 37-4).⁸⁴

Based on weak evidence from the above studies, GnRH agonist therapy appears to improve hirsutism compared to placebo, but there is no definitive evidence that add-on therapy to an OCP confers any additional treatment benefit. Furthermore, there does not appear to be

significantly greater efficacy with GnRH therapy compared to antiandrogens, although treatment benefits may be more sustained with GnRH agonists. The clinical utility of GnRH agonists is limited by their expense, the requirement for intramuscular or intranasal administration, and the need for estrogen supplementation to counteract their menopausal side effects such as hot flashes and emotional lability. GnRH agonists can also exacerbate acne and seborrhea and decrease bone mineral density (Table 37-2).

What We Know

- Glucocorticoids only modestly reduces hirsutism, and their side effects preclude their routine use for hirsutism except in the setting of classic CAH, and in those women with NCAH requiring treatment for infertility.
- The addition of glucocorticoids to antiandrogen therapy can prolong the duration of hirsutism remission.
- GnRH agonists may also prolong remission of hirsutism. Side effects and other more efficacious first and second line treatments, limit the use of these agents.

Are there any herbal supplements that can help reduce hirsutism?

Spearmint herbal tea has recently been shown to have antiandrogenic effects.⁸⁵ A trial by Grant randomized 42 women with PCOS to take either spearmint tea or a placebo herbal tea twice daily for 1 month.³¹ At the end of 30 days, androgen levels (free and total testosterone) were significantly reduced ($p<0.05$); however, there was no significant reduction in FG ratings ($p=0.12$). The latter finding was likely caused by the short duration of the study. The study findings are intriguing. Further trials of longer duration and basic studies regarding the mechanisms for spearmint's antiandrogenic effects are warranted.

TOPICAL MEDICAL TREATMENTS

Are topical therapies effective at reducing hirsutism?

Eflornithine 13.9% Cream

Eflornithine is an irreversible inhibitor of ornithine decarboxylase, the rate-limiting enzyme for polyamine synthesis and subsequent hair growth. Eflornithine 13.9% cream, when applied topically, reduces the rate of hair growth. There are two large industry-sponsored trials examining topical eflornithine for hirsutism. According to Wolf et al. (n=596, 395 women treated with eflornithine, 201 women treated with vehicle), eflornithine significantly reduced the growth and appearance of facial hair as compared to placebo after 8 weeks of twice daily application based on physician's global assessment, and this reduction was maintained for the rest of the treatment period of 24 weeks.⁸⁶ After treatment discontinuation, hair growth returned to pretreatment levels by 8 weeks. Adverse effects included pruritus and dry skin. In another trial, eflornithine treatment led to significant improvements in quality of life measures using the ESTEEM instrument to assess the psychological bother of hirsutism.⁸⁷ Furthermore, the ESTEEM instrument showed strong concordance with physicians' assessments using the mFG scale. Based on these studies, eflornithine reduces facial hirsutism in treated areas and has a minor side effect profile (Table 37-2). However, results are temporary and the treatment can be expensive. No studies have been conducted to evaluate safety in pregnant or in breastfeeding women. http://www.vaniqa.com/files/Vaniqa_Prescription_Info.pdf

Finasteride 0.25% Cream

Finasteride is FDA approved for androgenetic alopecia in men. Off-label use of a compounded finasteride cream for

treating hirsutism has been analyzed in one study. Lucas et al. performed a split-face study to examine the effects of a compounded finasteride cream (0.25%) versus placebo applied twice daily for 6 months in 8 unselected women with mixed etiology facial hirsutism or hypertrichosis (one woman) over 6 months. The study drug was compounded by grinding 15 tablets of finasteride (5 mg each) into propylene glycol and Dermabase (Paddock Laboratories, Inc.). Mean hair count decreased with finasteride treatment but not with placebo ($p<0.05$) and hair thickness also significantly decreased ($p<0.01$) on the side of the face treated with finasteride.⁸⁸ Finasteride cream is contraindicated in women who are pregnant or who may become pregnant. There were no significant treatment-related side effects. Although this study demonstrated treatment-related efficacy, the study was of poor quality with some women simultaneously taking an OCP or hormone replacement therapy. It is therefore, difficult to draw definitive conclusions based on such limited evidence. Further study may be worthwhile.

What We Know

- Finasteride topical cream cannot be recommended based on the available evidence.
- Eflornithine cream is a suitable and safe topical treatment option for hirsutism. Safety studies in pregnant women have not been conducted.
- Drinking spearmint tea lowers androgen levels. Studies have been of insufficient duration to adequately evaluate the effects of spearmint tea on hirsutism.

CONCLUSION

Most of the available evidence regarding various treatments for hirsutism including meta-analyses is based on original studies of low or very low quality and therefore, the evidence upon which recommendations are made is weak. Figure 37-5 provides a model for efficacy of systemic treatments for hirsutism based on the available evidence and Figure 37-6 provides treatment algorithms based on the above evidence. There are relatively few placebo-controlled RCTs with large sample sizes that adequately stratify patients according to their underlying etiology, and have methodologies of good quality. There are recognized limitations to clinician-assessed FG scoring, yet few studies actually measure patient-reported hirsutism outcomes and correlate these with FG score. The Endocrine Society's guidelines and commissioned meta-analyses for medical interventions are highly recommended sources for further information and guidance on the topic (Table 37-1).

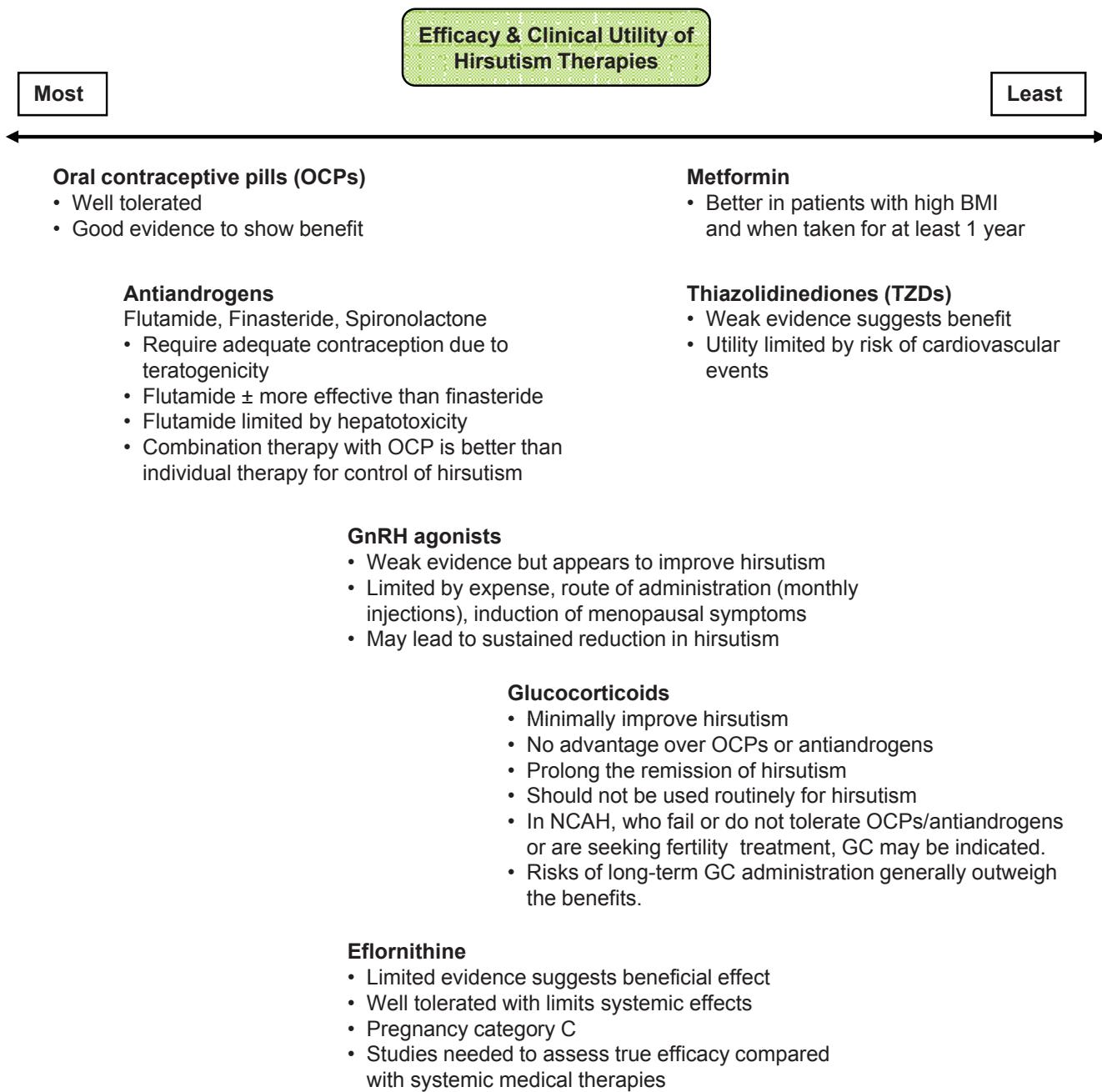


FIGURE 37-5 Evidence-based efficacy models for the systemic treatment of hirsutism.

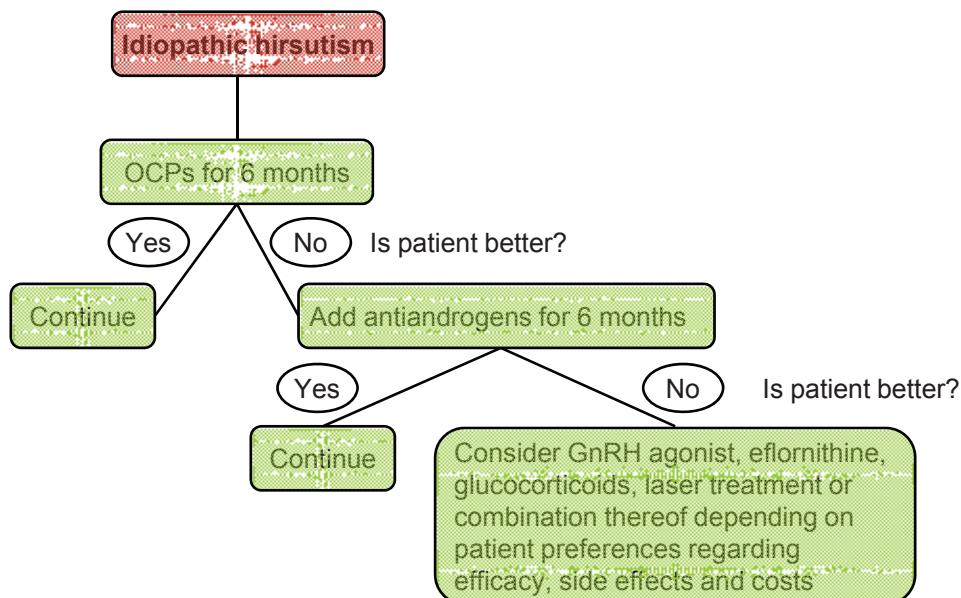
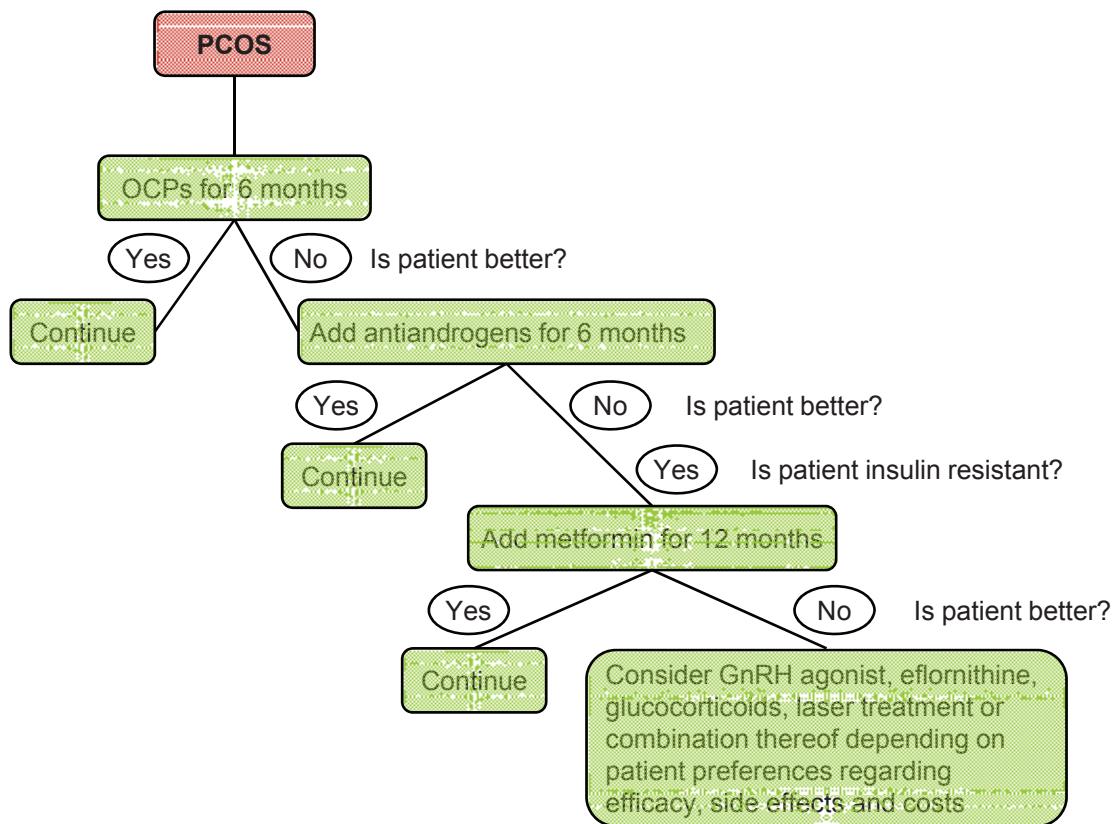


FIGURE 37-6 Evidence-based treatment algorithms for the medical treatment of hirsutism.

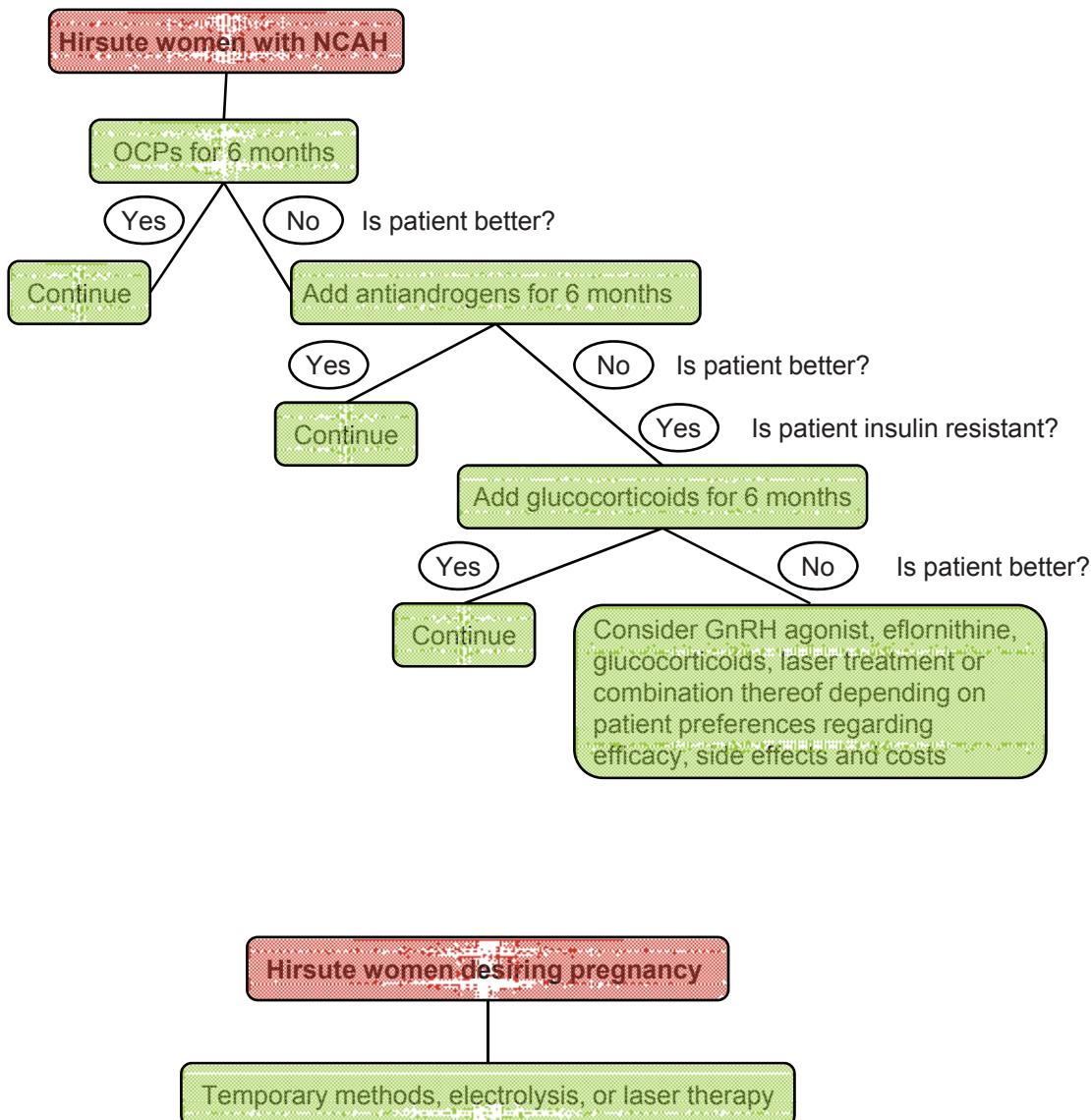


FIGURE 37-6 (Continued)

What We Know

- OCP therapy is associated with a significant reduction in hirsutism scores compared to placebo or no treatment. Recent guidelines recommend OCPs as the first line therapy for hirsutism given the teratogenic potential for antiandrogens
- OCPs should be chosen with a progestin component of low androgenicity or with antiandrogenic effects.
- Desogestrel, CPA, and DRSP containing OCPs are the best studied.
- Antiandrogens are an effective treatment for hirsutism (3 women need to be treated with spironolactone, flutamide or finasteride (NNT) for one to notice an improvement).²⁶
- Treatment with antiandrogens needs to be continued for at least 6 months to see a benefit.
- Flutamide may be more effective than finasteride but its risk of fatal and nonfatal hepatotoxicity limits its clinical utility compared to other antiandrogens.
- Antiandrogens can feminize a male fetus and must be used in conjunction with adequate contraception.
- Antiandrogens are more effective than metformin (NNT = 2 for flutamide vs. metformin; NNT = 5 for spironolactone vs. metformin)²⁶
- The addition of antiandrogens (spironolactone or finasteride) to OCPs is more efficacious than OCPs alone (NNT = 6)²⁶
- The addition of an antiandrogen (flutamide) to metformin is more efficacious than treatment with metformin alone (NNT = 2)²⁶

(Continued)

What We Know (Continued)

- Weak evidence shows limited to no significant beneficial effect of insulin sensitizers (metformin and TZDs) as a class for hirsutism.
- Although pooled studies of metformin show no beneficial effect on hirsutism scores, metformin may be beneficial in reducing hirsutism in overweight and obese patients with PCOS, especially those patients who have taken metformin for at least 12 months.
- Glucocorticoids only modestly reduce hirsutism, and their side effects preclude their routine use for hirsutism except in the setting of classic CAH, and in those women with NCAH requiring treatment for infertility.
- The addition of glucocorticoids to antiandrogen therapy can prolong the duration of hirsutism remission.
- GnRH agonists may also prolong remission of hirsutism. Side effects and other more efficacious first and second line treatments, limit the use of these agents.
- Finasteride topical cream cannot be recommended based on the available evidence.
- Eflornithine cream is a suitable and safe topical treatment option for hirsutism. Safety studies in pregnant women have not been conducted.
- Drinking spearmint tea lowers androgen levels. Studies have been of insufficient duration to adequately evaluate the effects of spearmint tea on hirsutism.

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Evidence-Based Procedural Dermatology

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Evidence-based procedural dermatology is finally no longer an oxymoron, but the road has been arduous and hilly terrain yet lies ahead. The inherent difficulties in advancing this field are largely the same ones that plague much of surgical research, regardless of specialty. In addition, there are peculiar obstacles to surgical research that are dermatology-specific. Finally, proceduralists themselves cannot be absolved of all responsibility. We sometimes suffer from reluctance to measure what we believe to be true. While this has been taken by detractors to be indicative of an anti-intellectual bent, the reality is quite the opposite. Surgeons are among the most therapeutically courageous, creative, and methodical dermatologists, but they are sometimes more inclined to invest their energies and intellect in improving procedures than in measuring the results.

DEFINITION OF PROCEDURAL DERMATOLOGY

For the purpose of this discussion, procedural dermatology may be defined to include minor and major invasive and noninvasive procedures performed by dermatologists. In concrete terms, these include several major categories of procedures, including skin cancer surgery and cosmetic procedures. Skin cancer surgery includes treatment of actinic keratoses with cryotherapy and photodynamic therapy; skin nonmelanoma skin cancer with electrodesiccation and curettage, excision, and Mohs; atypical nevi with excision; and melanoma with wide local excision and Mohs. Cosmetic procedures can be subdivided into energy procedures (laser, light, radiofrequency, ultrasound) that typically require large devices; minimally invasive cosmetic procedures (injectables and fillers, superficial peels and microdermabrasion, sclerotherapy); and major cosmetic procedures (ablative resurfacing with laser, peels or dermabrasion; rhytidectomy; blepharoplasty; endovenous laser or radiofrequency surgery, liposuction, large-scale skin reduction). In a nebulous area between cancer surgery and cosmetic procedures lie procedures pertaining to the removal of indefinitely benign but troublesome growths, such as cysts and lipomas.

THE MAKING OF A PROCEDURAL DERMATOLOGIST

To some extent, procedural dermatology has been defined by the availability of advanced training in the field. Apprenticeships with cosmetic surgeons and Mohs surgeons have been a staple of the past half century. Over time, these have coalesced into formal half-year or year-long training experiences.^{1,2} Professional organizations such as the American College of Mohs Surgery (ACMS, formerly ACMMSCO) and the American Academy of Cosmetic Surgery (AACS) have sought to standardize such training by creating clear expectations for training directors and trainees (e.g., fellows). More recently, in the past 5 years, an American Council of Graduate Medical Education (ACGME)-accredited fellowship in Procedural Dermatology has been inaugurated. Development of the guidelines for this fellowship has helped define the scope of advanced procedures in which dermatologists should have technical expertise. At times, a rancorous debate has ensued about which procedures are advanced procedures that so-called dermatologic proceduralists may consider their area of expertise, and which procedures are routine dermatologic procedures that are expertly performed by any dermatologist. Some maintain that no such distinction can be made and that no subset of dermatologists can claim any particular expertise in any particular procedure; procedures belong equally to all dermatologists. The countervailing argument has been that dermatology recognizes other clinically based subspecialties, such as pediatric dermatology and dermatopathology, and procedural dermatology, may have a similar claim when its practitioners have obtained additional training.

In any event, the term “procedural dermatology” is now used to signify both an area of dermatology (the subject of this chapter), and the clinical practice of so-called procedural dermatologists, and confusion can result. In the remainder of this chapter, the term will only be used to refer to the body of knowledge, and no implication will be made that any particular subset of dermatologists is more likely to successfully deliver any of the interventions subsumed in this category.

PROCEDURAL DERMATOLOGY IN THE DERMATOLOGY LITERATURE

Since the advent of the *Journal of Dermatologic Surgery and Oncology* (now *Dermatologic Surgery*) 35 years ago, procedural dermatology has had a friend in the medical literature. As Perry Robins relates it,³ when he founded JDSO, the prevailing view was amazement and a firm belief that he would be unable to fill it with articles of even dismal quality. This did not come to pass. More recently, during the past 10-20 years, there has been an upswing in the willingness of the principal general dermatology journals in the United States (e.g., *Journal of the American Academy of Dermatology*, *Archives of Dermatology*) to consider procedural manuscripts. No doubt, some of this sea change may be ascribed to the leadership of these journals; both Kenneth A. Arndt and June Robinson, collectively editors-in-chief of Archives for the past quarter century, are themselves pioneering proceduralists. There are also several other notable venues for procedural dermatology articles, including the *Journal of Cosmetic and Laser Therapy*, *Lasers in Surgery and Medicine*, and *Lasers in Medical Science*. Some other journals that have had many procedural contributions are the *Journal of Drugs in Dermatology*, *Journal of Dermatological Treatment*, and *Skin Therapy Letter*.

The procedural dermatology literature is evolving. There remains a brisk pipeline of articles pertaining to novel devices, especially laser and energy devices. As each such device is subtly different, and as there are no true generics for devices, trials must be repeatedly performed to establish the settings and parameters for efficacious treatment. The types of devices appearing frequently in the literature vary with the times. For instance 5-10 years ago, there was an abundance of articles about hair removal lasers; then came nonablative radiofrequency tightening devices and fractional resurfacing devices. An increasing number of articles now also address combination cosmetic treatments, such as those combining injectables with energy devices.

However, not all the notable articles of the past decade have been about cosmetic procedures. In the realm of cancer surgery, there has been a flurry of work pertaining to the treatment of skin cancer in transplant patients; the diagnosis and treatment of lentigo maligna and melanoma, including dermoscopy; and better understanding of management of rare tumors, like Merkel cell carcinoma.

MAJOR METHODOLOGIC ISSUES IN PROCEDURAL DERMATOLOGY

Comparative Studies

There are several major technical problems that have historically limited the rigor and hence authoritativeness of the procedural dermatology literature. One of these is the dearth of comparative studies that assess a novel intervention directly against an older procedure with a similar

indication. Thus, a study of a novel fractional laser resurfacing device may compare its benefits to the absence of any alternative treatment, rather than comparing it to an older resurfacing device, or some other resurfacing technique (e.g., medium-depth chemical peel), or even a placebo, such as an emollient. While this process of comparing treatment to no treatment can result in detection of a large effect size (i.e., relative benefit for the treatment arm), this may still not induce a change in clinical management, since the alternative treatment is rarely to do nothing, and the prevailing standard-of-care treatment may be as good as the novel experimental treatment. Moreover, comparisons to lack of treatment do not account for placebo effect. That is, when patients are provided a free procedure, as in the case of many studies, they are prone to see a significant benefit even when little or no benefit objectively exists. This overestimate of efficacy is not a deliberate attempt to deceive, but rather may be an expression of gratitude for the free treatment, a desire to please the investigator, or a form of self-reassurance that the pain and inconvenience of the procedure were worthwhile. Comparing one procedure to another procedure may mitigate the placebo effect. Of course, sometimes this can be infeasible, and it is not always possible to do a sham procedure that looks and feels just like the experimental procedures. To wit, patients who get petrolatum to one area and laser to another will know which side received the “real” treatment, and therefore be subject to a significant beneficial placebo effect on that side versus the other side; similarly, if an ablative laser is used on one side and a nonablative laser on the other, the sensations will be markedly different, as will the appearance of the skin post-treatment.

Power and Sample Size

Another significant methodologic concern is the need for adequate sample size in studies of procedures.⁴ Sample size is intimately related to effect size and power. Intuitively, the bigger the difference expected between the efficacy of two procedures (i.e., the larger the effect size), the fewer subjects will be needed to show this is the case (i.e., the smaller the sample size that will be needed). Power refers to the level of surety that a given real difference will be detected with a particular sample size; if the investigators want to be extremely sure that no difference is missed, they select a high power (e.g., 0.9 rather than 0.8), which will require a correspondingly larger sample size. Primarily, procedural dermatology studies suffer from underpowering. Part of the problem is that many studies are commenced without even attempting a power study; investigators just select a number that *prima facie* appears reasonable to them, or they enroll as many as they can. This many is frequently not enough. When a power study is performed, the projected sample size may not be practical to achieve. It can be onerous to collect a large number of patients at just one site. Moreover, multicenter trials are difficult to

perform, given the incompatibility of sparse funding for clinical research in procedural dermatology and the ever-burgeoning additional costs of cross-center collaborations mandated by health insurance portability and accountability act (HIPAA) requirements and ever-expanding institutional review board (IRB) strictures. However, even when patients are available and costs not prohibitive, it may be challenging to correctly power a study in the absence of prior research with which to estimate effect size. Since clinical research in procedural dermatology is young, often there are no older similar studies on which to base assumptions. This ambiguity may engender overly rosy guesses: when you do not know how many you need, you might as well make it easy for yourself and go with the lower number.

Measurement of Outcomes

A related obstacle is the subjectivity and imprecision of the outcomes to be measured. For instance, in a cardiology study, outcomes such as death or left-ventricular ejection fraction are precisely measurable. In procedural dermatology, on the other hand, outcome measures for cosmetic trials can be such vague constructs as patient satisfaction, or degree of improvement in appearance of photoaging. For cancer reconstruction trials, the outcome may be the attractiveness or imperceptibility of the scar. Indeed, the FDA has been reluctant to grant any device an indication for “skin tightening” in large part because no rigorous definition for this amorphous outcome has been put forth. Procedural dermatology outcomes are often qualitative, ordinal, or categorical, not dichotomous or continuous. This complicates estimation effect size and power, and the overall utility of the trial. To a large extent, obtaining useful information from a procedural dermatology study is contingent on the training and skill level of the blinded raters used to assess the subjective outcome. If they are ill trained, distracted, or imprecise, it may be impossible to detect an effect regardless of the patient number. Similarly, the skill level of the surgeon performing the procedures is a variable that can skew outcomes. If chemical peels are being compared to laser resurfacing for efficacy in treatment of acne scars, it will be important to ensure that all the operating surgeons are equally expert on both procedures, so that the outcomes are a reflection of the difference between modalities and not of the surgeons’ limited skills in one area. Finally, sometimes the real difference being examined in a procedural trial is so small that a subjective measure is unlikely to be able to elucidate it. For instance, even in the best hands, two materials for soft-tissue augmentation may be so similar that patient differences, injection technique, and other factors outweigh any inherent difference between the products. As there are no generic devices, and every maker touts their own iteration as the superior version, many cosmetic surgery trials are designed to compare two devices (e.g., hyaluronic acids, or fractional lasers) that use

the same underlying technology; such trials can be remarkably uninteresting when not much difference is found.

Some investigators have worked hard to improve the quality of outcome assessment. Thus, precise measuring devices, like ultrasound scanners and 3-D animations, have been used to map and compare differences too small for the naked eye to detect. The caveat here is that it is hard to give credence to the output of a measurement device that has not been validated, as it is certainly possible for such a device to generate precise measurements that are neither reproducible nor accurate. A stronger critique is that even if the machine detects a “real” difference, this may not be interesting if no human, even with the best eyesight under optimal conditions can corroborate the change. It seems unreasonable to advocate that a patient obtain a cosmetic procedure that is ostensibly superior when none of their friends, family, or acquaintances will be able to distinguish it from a less expensive, older one. That is not to say that the best measure of a cosmetic or reconstructive procedure is patient self-assessment. Patient assessments are notoriously inaccurate, almost invariably inflated for several reasons: (1) a desire to please the investigator, who may also be their personal physician; (2) an expression of gratitude for a free procedure to reduce the visible signs of aging or restore function; (3) an expectation that the discomfort and inconvenience associated with the intervention would necessarily result in aesthetic improvement; and (4) lack of numeracy and quantitative skills, which exacerbates the tendency to overestimate improvement.

From a philosophical standpoint, the best assessment of the efficacy of a cosmetic procedure remains whether the patient looks better after than before. Practically, the least biased, most valid measure of improvement currently available is probably blinded rater assessment. The quality of the rater is important, and in general, board-certified, experienced dermatologists are more credible than residents and fellows in training, medical students, and other well-intentioned bystanders. Having more than one rater may minimize the disproportionate effect of one rater’s preferences: personal standards of physical attractiveness may play a role in evaluating any cosmetic outcomes, even when no overt bias is present. On the other hand, multiple raters do increase study complexity and cost, and raters may not agree. Statistical tests can be performed to assess the degree of inter-rater agreement. An alternative method that has been accepted by FDA for device clinical trials is “forced agreement.” In this approach, multiple raters score an outcome independently, and then meet to debate and resolve any discrepancies.

A major obstacle to blinded rater evaluation is that the process can undermine the quality of the data being assessed. It is difficult to maintain blinding during live subject examination; additionally, live examination precludes comparing before and after results side-by-side. So photographs are typically used. Nevertheless, even high quality standardized photographs taken from several vantage points have flattened

topography, limited contrast, and artificial hue compared to the original. Three-dimensional representations can be created to overcome these limitations, but these constructs are also a proxy for the real thing, and not as good. Notably, in many procedural studies, single- or rater-blinding is the best that can be managed. This derives from the nature of the underlying procedures, which often preclude patient blinding. One laser may not feel like another, and one excisional technique may take longer, require different equipment, and leave a different scar than another. The obvious solution, sham surgery on the control side, is often infeasible, and requires a very convincing rationale to survive IRB review.

Statistical Methods

A final limitation that pervades many procedural dermatology studies is inadequacy of the statistical section. In some cases, statistics are not necessary. For example, papers that elucidate surgical technique, or those that survey a subset of proceduralists, may only provide descriptive statistics, such as the percentage of a certain procedure associated with complications, or the number of Merkel cell carcinomas treated by a cohort of dermatologists in Indiana in 2008. However, very often, some statistical analysis is desirable. This can be facilitated by enlisting the services of a good biostatistician, who may be available from a local university or an affiliated comprehensive cancer center. Indeed, before even commencing a study, it is very useful to write a complete protocol itemizing exactly what is to be done, the types of data to be collected, and the main outcome measures. At this point, before a single patient is enrolled, the biostatistician can not only provide a power study and sample size estimate, but also confirm that the data will be analyzable to yield information of the type desired by the investigator. If the statistical analysis is post-hoc, the statistician can still explain what can be analyzed. It is often helpful to formulate questions that the investigators would like the study data to answer. The biostatistician can then organize the data in an appropriate manner, apply the necessary statistical tests, and explain the findings. Typically, in procedural dermatology studies that do include statistical analyses, p-values are listed to demonstrate statistical significance or lack thereof. While this can be helpful, it is also valuable to list 95% confidence intervals of the key measures. Confidence intervals are an intuitive way to display the likely range of a given variable, and compare it to other variables.⁵ To wit, let us say that eating beets reduces new actinic keratoses to 3 a month but excision cuts down the rate to 1 per month, $p=.42$. On a cursory read, it is easy to mistake the difference between one and three as clinically significant, or to be baffled as to why the p-value is so high. But if the confidence intervals are listed, and it turns out that the likely true efficacy range of excision is 1 ± 4 (95% CI: -3 to 5), and of beets, 3 ± 2 (1 to 5), it becomes obvious that the overlapping of

the confidence intervals means no persuasive difference has been detected. Confidence intervals are as yet reported infrequently in procedural dermatology trials.

An important distinction rarely tackled is the difference between statistical significance and clinical significance. A study that does not detect a statistically significant difference cannot be said to have found a difference of clinical significance. However, even if a statistically significant difference is revealed, it may not be clinically significant. The subjective nature of many outcome measures in procedural dermatology makes this problem worse. As an example, let us say an ultrasound-tightening device results in 45% improvement of fine wrinkles, but a radiofrequency device provides 55% improvement, with this difference being statistically significant. It remains unclear whether the difference is clinically significant, as it is uncertain to what extent patients value a 10% difference in wrinkles, and to what extent a decrement of 10% is associated with objective harm. A related issue is willingness-to-pay. Willingness-to-pay is a measure of the value in dollars that patients hypothetically ascribe to a given outcome. In our example, we would like to know how much patients are willing to pay for the 10% wrinkle reduction possible with the more efficacious device. A high enough amount may make the radiofrequency procedure desirable even if it is more expensive; but if the patient premium for the incremental 10% benefit is low, patients may prefer to forego a more expensive radiofrequency procedure for a cheaper ultrasound procedure.

Randomized Control Trials, Structured Reviews, and Meta-Analyses

Randomized trials are probably more feasible and hence more common for comparing cosmetic dermatologic interventions. Here, however, there are problems associated with recruitment and loss to follow-up. Cosmetic patients are often not willing to endure the perceived indignity of being in a study, and may be willing to pay full price to avoid this. They want what they want, when they want it, and are at variance with the traditional medical model, in which a compliant patient is beholden to the physician for improving their health. Potential patients may also be reluctant to receive placebo, or worse yet, undergo a split-body randomization, in which part of their skin surface may be improved, but part left unchanged. No one wants to be asymmetrical, especially when the purpose is betterment of appearance, not disease amelioration. Furthermore, when patients do enroll in cosmetic trials, they may be highly susceptible to dropping out. Once the intervention has been received, they have limited incentive to return for follow-up visits to assess treatment efficacy and longevity. Studies that are conservatively designed with an “intention-to-treat” methodology, which includes all randomized patients in the final analysis, may see their results weakened to nonsignificance by this problem. More patients

can be recruited, but this is not easy either, as explained before.

Meta-analyses are studies that combine and re-analyze the data from multiple randomized trials on same question. Structured reviews also evaluate evidence from many similar studies, ideally mostly randomized-controlled trials, but such reviews do not necessarily re-analyze any data. To the extent that there is a dearth of randomized-controlled trials in both skin cancer and cosmetic surgery, there is limited substrate for creating meta-analyses and structured reviews. This means that many important questions cannot be definitively answered, with conflicting low-level evidence forcing every physician to make their own judgments. Clearly, there is a need for more randomized trials. Additionally, it would be helpful if there were some coordination among investigators, such that the most vital questions were studied first, and each in several independent studies. There have been some efforts to unite data collection for procedural dermatology trials across centers; for instance, the Sulzberger Institute of the American Academy of Dermatology has funded the Dermbase project, which creates a web-based interface for prospective multicenter data collection.

TOPIC-RELATED LIMITATIONS

Cosmetic and Laser Surgery

Procedural dermatology is comprised of subfields, and the most notable division is between cosmetic dermatologic procedures and skin cancer surgery. Each of these is associated with specific challenges that complicate the prosecution of high-quality research. Cosmetic dermatology suffers from problems with patient recruitment. Cosmetic patients from one's own practice may be the easiest to recruit for studies since they have a pre-existing relationship, and are likely to follow instructions and return for follow-up visits. However, this same relationship may lead these patients to provide an overly optimistic judgment of the efficacy and tolerability of a procedure. Recruiting cosmetic patients from newspaper advertisements and public postings is fraught, because this results in many patients willing to receive a free cosmetic procedure but unwilling to follow-up, and because myriad screen failures (e.g., patients who come in to be evaluated but do not qualify for the study) can make an underfunded cosmetic study even more financially unsound.

As noted in the preceding section, outcomes of cosmetic procedures are especially difficult to measure in a meaningful way. In part, this is because aging is not classified as a disease. Therefore, it is necessarily difficult to compare the visible signs of aging to those of a "non-disease" benchmark for similarly aged patients of similar stature, gender, and ethnic type. Since patient features cannot be compared to fixed reference points (e.g., as in the assessment of blood pressure), we are limited to comparing preprocedure

features to postprocedure features. Patients continue to age while these procedures and comparisons are performed, thus further complicating the comparison. In fact, cosmetic dermatology studies often have a relatively short follow-up period for this reason: over the long-term, whatever the benefits of the intervention, they are overwhelmed and subsumed by the relentless deterioration of the aging body. Follow-up may also be abbreviated for other reasons: (1) subjects may after a few months choose to receive other noninvestigational cosmetic procedures, which can obscure measurement of the effects of the initial intervention; and (2) some cosmetic procedures intrinsically have a short half-life. Short follow-up periods can be problematic for tightening, filling, and wrinkle reduction procedures in which immediate postoperative edema, which soon remits, can be mistaken for a successful outcome.

In addition, with cosmetic surgery studies, there are problems pertaining to conflict of interest. Cosmetic interventions often require devices, which range in complexity from syringes containing temporary filler pastes, to lasers and energy devices comprised of hundreds of parts. Most of these devices are developed by commercial entities, which in turn enlist dermatologists to study their use. Often the physician leaders in device research derive significant revenue from the manufacturers and distributors of the corresponding devices, so creating a situation in which the investigators may be vulnerable to conscious or unconscious bias to selectively detect high levels of device efficacy. Demands to eliminate such conflicts are unrealistic because virtually all the leaders in cosmetic device research have multiple relationships with industry. Moreover, it is not clear whether an investigator who has a low level of familiarity with a new device, or who has not previously worked to develop and test similar devices, would be able to execute a clinical trial that best utilized the device to attain a given clinical endpoint. Significant background knowledge appears to be a prerequisite for optimally adapting a device for a particular indication. Nonetheless, the charge that the underlying conflicts do sometimes detract from the transparency of the research is a troubling one, and difficult to disprove.

Skin Cancer Surgery

Studies of skin cancer surgery and reconstruction are also associated with specific challenges and limitations. In a common type of cohort study, surgeons describe a number of patients who have undergone a novel procedure, or a procedure at least partially modified from the standard approach. Such studies are always at risk of degenerating into anecdote. Case series or cohorts may be from a single center or refer to procedures performed by a single surgeon, with this structure rendering them susceptible to selection bias and limiting their external validity.⁶ An associated issue is that large series may pull patients from many

years, even decades, and the surgical methods may have evolved or changed over this duration.

Well-controlled cohort studies and randomized control trials have some of the same problems. In all of these, it is quite common to have inadequate methods sections that do not fully describe, in minute detail, the exact surgical approach. Thus, even if the reader is convinced of the efficacy of a surgery, replicating this clever solution may be impossible without contacting the authors for additional information. It may also be difficult to completely account for the idiosyncrasies of specific surgeons, and to generalize to a hypothetical standard surgeon. Well-designed prospective studies do attempt to enroll multiple qualified surgeons, and even to provide consistent training to these, but surgeons are not robots, and all surgeons have strengths, weaknesses, and biases that predate the inception of the study. Not every hand movement can be prescribed, not every scalpel cut can be standardized, and not every surgeon handles tissue equally gently. A study may find a procedure to be of limited benefit not because the procedure is inherently flawed, but because the surgeons who performed it may not have been best suited to making it more successful.

Some limitations of skin cancer research are exogenous to dermatologic surgeons. Thus, randomized-controlled trials to assess novel treatments for nonmelanoma skin cancer are elusive because highly effective, nonexperimental treatments already exist. Indeed, it is unlikely that treatments can be devised that are *more* effective than Mohs surgery, which in some studies has a cure rate of in excess of 99% for primary basal cell carcinoma. Experimental nonmelanoma skin cancer treatments may have benefits in terms of patient convenience or cost savings. However, these benefits are much harder to elucidate in a well-designed study; convenience is a fungible concept, and aggregate cost includes indirect costs, such as “shoe leather” costs associated with repeated patient appointments, daycare costs, and the like, which are hard to gauge precisely. Novel cancer treatments may be most useful for rare or aggressive skin cancers, which are less amenable to standard therapy. However, the very rarity of these cases makes a randomized control trial difficult to perform.

FUNDING SOURCES

Funding for procedural dermatology studies is sparse, sporadic, and unpredictable. Nonmelanoma skin cancer, and even early, primary melanoma, does not elicit much enthusiasm from federal funding agencies. In the absence of significant nonmelanoma skin cancer-associated mortality, procedural dermatologists are forced to highlight the associated quality-of-life impact,^{7,8} which is not considered as persuasive by nondermatologists. Appropriate metrics have not been developed to sum the aggregate quality-of-life decrement among literally tens of millions of nonmelanoma skin cancer patients in the United States.

So-called “utility” measures, which can compare quality of life across disparate disease states, remain controversial. As a consequence, funding for nonmelanoma skin cancer research has been very limited. Veterans Administrations grants, Dermatology Foundation grants, and modest local funding has supported the preponderance of clinical research in this area. Research on topical prophylactic medications, such as imiquimod, has been bankrolled by manufacturers, but as discussed before, this can hardly be considered an unbiased approach.

In the realm of cosmetic procedural dermatology, the situation is even grimmer. Apart from research underwritten by device manufacturers, there is little clinical research of any sort in this area because of the lack of other funding sources. Dermatology Foundation career development grants on the science of human appearance are welcome, but data from these projects cannot be leveraged to obtain federal funds, which are not at all forthcoming in this area. Minute professional association grants, like those from the American Society for Dermatologic Surgery and the American Society for Laser Medicine and Surgery, can initiate interesting routes of inquiry, but not sustain them. Paradoxically, the extremely high level of safety associated with cosmetic dermatologic procedures has reduced the urgency to study these. The one moderately well-studied cosmetic procedure is liposuction, which has elicited this special attention because of a misunderstanding on the part of regulators and the general public regarding the risks of tumescent liposuction versus liposuction under general anesthesia; that is, tumescent liposuction is exceedingly safe, but we in dermatology have had to substantiate this in the face of unsupported misinformation. However, the safety of other cosmetic procedures should not diminish our interest in studying them. Efficacy, longevity of effect, convenience, level of discomfort, cost, and other similar parameters can be used to distinguish between high quality and less successful cosmetic procedures. In this vibrant, ever-changing area, such research can also help ensure that successive devices are better, and not merely different.

ADVANCES IN EVIDENCE-BASED PROCEDURAL DERMATOLOGY

It is easy to lose the forest for the trees. While there is much in procedural dermatology that could be better, during the past several decades, the field has made enormous advances. Virtually all cosmetic laser devices and most fillers and injectables were developed and refined by procedural dermatologists. In the skin cancer realm, proceduralists have drastically reduced with Mohs the recurrence rates associated with nonmelanoma skin cancer; they also perform more facial reconstruction than all other medical specialties combined. For the most vulnerable patients, such as organ transplant recipients, procedural dermatologists have clarified optimal diagnosis and treatment regimens.⁹ Perhaps most notable among the

achievements that can be ascribed to procedural dermatology is the conclusive determination that complex cancer and cosmetic surgeries can be safely performed under local anesthesia.¹⁰ The body of knowledge now clarifying this beyond a shadow of a doubt is truly immense. Indeed, even invasive procedures such as liposuction can be performed *more* safely under local anesthetic in an office setting than under general anesthesia in a traditional operating room.

Journals that publish procedural dermatology articles have helped to improve the quality of research in this area. For instance, *Dermatologic Surgery*, historically the principal repository for the procedural dermatology literature, has de-emphasized anecdotal "how I do it" type articles in favor of articles that attempt to describe the utility of a procedure in more systematic manner. Peer review has become more stringent as the number of procedural dermatologists has grown, and the specialty has become large enough to field numerous experts in various sub-fields and topic areas. The quality of some research in procedural dermatology has risen to the point where it has found a home in the well-regarded general medical literature, including journals such as *Cancer* and *JAMA*. The breaching of this glass ceiling is a source of encouragement to young investigators.

In the future, such young investigators may help transform this field. Historically, in academic procedural dermatology, a single procedural dermatologist or dermatologic surgeon was responsible for performing surgery, teaching residents, administering staff, and occasionally writing a paper or two. Over the past 10 years, many university dermatology departments have acquired two or more dermatologic surgeons. As the number at some centers moves to three and more, it becomes possible for one or more surgeons to be freed of many routine clinical and teaching responsibilities so that they may devote more time to research. This research can be internally funded, by a tax on surgery section revenues, or by external grants, which may be easier for an applicant to garner if 70-80% of effort is protected for research. Based on this model, notable efforts to perform population-based research have been

undertaken at Kaiser Permanente in California, and at the Mayo Clinic in Rochester. Various centers, the University of Michigan being the most prominent, have been successful at creating an incubator for academic procedural dermatologists with a research focus. A number of procedural dermatologists have now acquired advanced training in clinical epidemiology and health services research; for perhaps the first time, young trainees are deliberating embarking on this path early in their careers, hoping to become the research pioneers of tomorrow.

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Treatment of Unwanted Hair (Nonmedical Interventions)

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INTRODUCTION

Patients seeking treatment for unwanted hair has become one of the most common reasons for dermatologic consultation. The causes of hirsutism and hypertrichosis are numerous, including heritable factors, endocrine disorders, and exogenous drug therapy.¹ Increased hair density in men and women may be localized or generalized. Patient concerns related to hair removal treatment include clinical efficacy, safety, expense, convenience, associated pain, and other short- and long-term side effects.

ANATOMY OF THE HAIR FOLLICLE AND HAIR GROWTH

The hair follicle can be divided into four distinct regions—bulb, suprabulbar zone, isthmus, and infundibulum. The actively growing portion of the hair is the matrix, which along with the dermal papilla, comprises the hair bulb. Matrix cells rapidly divide, migrate upward, and are confined to the lowermost portion of the follicle. The isthmus of the follicle is the short portion located between the point of attachment of the arrector pili muscle and the entrance of the sebaceous gland duct. The infundibulum lies above the entry of the sebaceous duct to the hair follicle orifice and merges with the epidermis.

Actively growing (anagen) hairs are characterized by a hair matrix surrounding a dermal papilla with well-developed inner and outer root sheaths. On the scalp, a typical anagen follicle produces a hair shaft for approximately 2 to 3 years—giving rise to longer hair. The shorter hairs found in other body locations have correspondingly shorter anagen periods. Dying or regressing (catagen) hairs are identified by markedly thickened vitreous layers and fibrous root sheaths surrounding an epithelial column, above which the presumptive club forms. The catagen stage of the hair cycle lasts for only a few weeks and ends as the hair enters into a “resting” (telogen) stage. A telogen hair has a fully keratinized club, which is surrounded by an epithelial sac. Below this lies the secondary hair germ and condensed dermal papilla.² New anagen hair growth is initiated by cells that reside in the bulge region—the protuberance of cells that serves as a point of attachment for the

TABLE 39-1—Hair Growth by Body Location

Body location	% Anagen hair	Telogen stage
Beard	70	10 weeks
Upper lip	65	6 weeks
Axillae	30	3 months
Arms	20	18 weeks
Legs/Thighs	20	24 weeks

arrector pili muscle.³ During the 3 months of telogen, the bulge lies near the secondary hair germ.

The majority of hair follicles (80–85%) on the scalp are in the anagen phase and the remaining follicles are either in the catagen (2%) or telogen (10–15%) phase. On other areas of the body, anagen hairs may account for only 20–50% of the total number of hairs present. Telogen may last for a couple months on the face and for many months on the upper arms and legs⁴ (Table 39-1).

Anagen hairs vary in size from the large terminal hairs found in the beard and on the scalp to fine vellus hairs covering most of the glabrous skin. Vellus and terminal hairs go through all stages of the follicular life cycle, but the length of anagen is much shorter in vellus hairs. Although vellus hairs cover most of the human body, terminal hairs are of more interest to both the clinician and patient as their presence is more noticeable in hirsute conditions².

TEMPORARY METHODS OF HAIR REMOVAL

Bleaching

Bleaching lightens the color of the external hair shaft to make it less noticeable without physically removing the hair follicle. This method is best used for the treatment of excess pigmented hair on the face or arms of fair skinned patients. The contrast of yellow bleached hair against the skin of darkly pigmented patients is highly visible and is therefore not suitable in these skin types. Several types of commercial hair bleaches are available: neutral oil bleaches, color oil bleaches, cream bleaches, and powder bleaches—all of which contain hydrogen peroxide as the active ingredient.

While a 6% concentration of peroxide bleaches, softens, and oxidizes the hair, the addition of 28% ammonia accelerates its bleaching action. The addition of persulfate to intensify peroxide hair bleach has resulted in generalized urticaria, asthma, syncope, and shock in sulfide-sensitive patients.⁵ While bleaching is a quick, painless, and relatively inexpensive process that can last up to 4 weeks, disadvantages of its use include skin irritation, hair discoloration, and a lack of desired efficacy.^{6,7} Bleaching should not be performed on skin that is broken or has signs of infection.

Trimming

Trimming of hair is the treatment of choice for young children with either localized or generalized hypertrichosis. It is safe and does not accelerate hair regrowth.

Shaving

Shaving is one of the oldest and most frequently used methods of hair depilation. Shaving is usually performed with a manual or electric razor on skin that is wet and lathered or covered with a special foaming product. Contrary to popular belief, shaving does not affect the width or rate of regrowth of individual hairs⁸; however, the rough stubble following shaving may be undesirable. Safety razors have been preferred over electric razors by both men and women because a closer shave can be achieved. Although most women report little difficulty shaving their legs, it remains an unpopular method for the removal of unwanted facial hair. Shaving is convenient and of low cost; however, its disadvantages include abrasions, stubble, and skin irritation, which can develop into pseudofolliculitis barbae (PFB). PFB is common in men of African heritage and can be prevented with a less clean shave. Extreme cases may require treatment with corticosteroids, retinoic acid, or laser-assisted hair removal (see below).

Tweezing

Tweezing or plucking is a temporary and effective method to remove a small number of hairs. Tweezing lasts longer than shaving because the hair is extracted from the follicle in its entirety as opposed to being cut at the surface of the skin. Anagen hair bulbs tear in reproducible patterns which include the typical break conically surrounding the dermal papilla, rupture of the hair around the upper third of the papilla or well above the papilla, or total removal of the proximal follicle epithelium with removal of the dermal papilla.⁹ Drawbacks include treatment discomfort and risk of folliculitis, hyperpigmentation, erythema, follicular distortion, and scarring.^{5,6} Alteration of the mesenchymal sheath of the hair follicle may also lead to pinpoint hemorrhages and perifollicular edema. While rare, plucking of hairs from melanocytic nevi may result in the development of foreign body granulomas

around disrupted hair follicles which can develop into Nanta's osteonevus (metaplastic ossification).¹⁰ Electronic tweezers provide an inconsequential transmission of electric current into the follicle with subsequent rapid hair regrowth. Erroneously believed to be a permanent means of hair removal, its use has declined after the Food and Drug Administration (FDA) reported it is "no better than nonelectrified household tweezers."¹¹ They also emit measurable levels of radiation and are not recommended for use by pregnant women or those with pacemakers.

Mechanized tweezers with a rotating, fine, coiled spring can grasp and pull out the hair shaft for more diffuse areas of hypertrichosis, most commonly on the legs. The hand-held device is relatively easy to operate, but can be painful due to large areas of synchronous epilation.

Waxing

Waxing provides a uniform method of plucking hair. The technique involves the application of melted wax to hair-bearing skin. Upon drying, the wax is rapidly peeled away from the skin in the direction opposite to hair growth. Care should be taken during application because excessively hot wax can cause thermal burns to the skin. Although waxing can be used to remove unwanted hair in every skin type and any hair length, best results are obtained when the hair is trimmed to a quarter of an inch in length prior to waxing. Waxing is inexpensive and the results are longer-lasting than with shaving or chemical depilatories because hairs are removed from the hair bulb rather than at the skin surface. Six weeks of relatively hair-free skin is typically achieved.⁵

Cold semisolid waxes are also available, but are usually more expensive and cannot be reused. Potential allergic sensitizers in waxes are beeswax, rosin (colophony), fragrance, and benzocaine.⁵ In addition to treatment discomfort, waxing has been reported to cause folliculitis, skin irritation, and keloid scars.^{6,12} The long-term effects of waxing on the follicle are not known, but many patients use it repeatedly for several years without experiencing significant problems. It may even be possible to reduce the amount of hair regrowth due to repeated waxing-induced follicular trauma.⁶

The non-Western technique of sugaring is another temporary hair removal method. Sugaring is similar to waxing except that a sticky paste is applied to the skin instead of melted wax or a cold polymer. The paste is formed by mixing sugar, water, lemon juice, and gum arabic or gum ovaline and heating it until the mixture forms a syrup. Sugaring is often preferred for large surface areas, such as the back or legs.

Mechanical Epilation

Mechanical abrasives come in many different forms and range from pumice stones and abrasive gloves to small sticks or wands lined with fine sandpaper. The skin is

held taut with one hand while the other rubs over a hair-bearing area in a circular motion to remove hair at the skin surface. Skin irritation and follicular distortion are common side effects of this treatment and is, thus, seldom used.^{5,6} Traumatic folliculitis has also been reported from home epilation devices that produce skin surface friction via circular motions over hair-bearing areas.¹³

Threading, also known as “banding,” is a method of hair removal used extensively in Arabic countries. A fine cotton string is used to capture hairs, which leads to removal of some hairs at their roots while others are simply cut off by the scissoring action of the twisted thread. Clinical results usually last 2 to 6 weeks. Side effects include folliculitis, erythema, and secondary pigmentary changes.^{6,14}

Chemical Depilatory Agents

Chemical depilatories exert their effects through separation of the hair from its follicle and the surrounding skin surface by reduction of disulfide bonds. Because the hair shaft is composed of more disulfide-containing cysteine than is epidermal keratin, sulfur compounds of calcium, arsenic, antimony, barium, and strontium can effectively dissolve the hair shaft.^{5,8} Newer chemical depilatory agents contain mercaptan thioglycolic acid mixed with alkali.⁸ With these formulations, the hair shaft is hydrated and disulfide bonds broken. Since chemical depilatories frequently penetrate into portions of the infundibulum, it usually takes several days before any hair regrowth is observed.⁵ Therefore, chemical depilatories are most appropriate for weekly hair removal from small areas.

An irritant contact dermatitis caused by the alkalinity of chemical depilatories is the most frequent adverse reaction and can be avoided with the concomitant application of a topical corticosteroid. Allergic contact dermatitis may also occur because of the presence of fragrances in the preparations and cross-reactions have been observed between mercaptan and dimercaprol.⁵ Less than 1% of patients are thus able to tolerate facial application of depilatories. Additionally, many find the procedure to be excessively messy and the depilatory’s smell offensive.⁶ Thioglycolate-containing depilatories are not recommended for men’s beards because they do not penetrate the hair shafts quickly enough to be a practical alternative to shaving.⁸ Although strontium and barium sulfides are effective in this setting, the hydrogen sulfide gas released by these compounds yields an unpleasant odor. In addition, barium sulfide is more irritating to the skin than the more commonly used calcium thioglycolate.

Surgery

Surgical excision of axillary apocrine glands in patients with hirsutism and hyperhidrosis has been found to cause hair loss in the area.¹⁵ Eventual hair regrowth may be expected because of the varying depths of anagen, catagen,

and telogen hair follicles. The scars that result from surgery are often a major obstacle because of their cosmetically unacceptable appearance.

Radiation Therapy

In the 1920s, hypertrichosis was managed with x-ray treatment resulting in radiation-induced cutaneous malignancy, including basal cell carcinomas, trichoblastomas, and trichoblastic carcinomas on the scalp with a mean of onset of tumor development of 39.4, 38.3, and 35.6 years, respectively.¹⁶ Although more than 80% of the x-ray treatments were performed before 1930, reports persisted into the 1940s with multiple basal cell carcinomas and a spindle cell carcinoma documented 52 years after x-ray epilation of the limbs.¹⁷ As safer treatment alternatives were introduced over the years, radiation therapy fell out of favor and is not currently considered an acceptable treatment option for hair removal.

PERMANENT METHODS OF HAIR REMOVAL

Electrolysis and Thermolysis

Electrolysis, thermolysis, and a combination of both are three popular procedures used for epilation or permanent hair removal and are performed more often in the United States than anywhere else in the world.⁵ All three methods involve the insertion of a small needle or probe into the hair follicle through which an electric current is delivered, resulting in the production of a microscar that surrounds the follicle, but is barely perceptible at the skin surface.¹⁸ Focal erythema and edema following treatment usually resolve within a few hours.¹⁹

Electrolysis is performed by passing low flow direct or galvanic current through tissue between two electrodes which causes a chemical reaction to occur at the electrode tip, resulting in tissue damage and destruction of the hair follicle. The production of local hydroxides destroys the hair bulb and enclosed dermal papilla. While galvanic electrolysis is effective, it is a slow process, requiring a minute or more for each hair.²⁰ Its advantage lies in its ability to effectively treat curved or distorted follicles because hydroxyl ions, being in a fluid medium, can flow to all portions of the follicle.¹⁹

Thermolysis (diathermy) is performed using high-frequency alternating current at low voltage to thermally destroy or epilate hair follicles—a process termed electroepilation. Thermolysis has a somewhat higher risk of scarring and pain, although modern electroepilation devices have precise automatic timers and insulated probes that reduce the risk of scarring.²¹ The process requires only a few seconds per follicle and is much faster than galvanic electrolysis; however, the results are not as consistent, particularly when treating distorted or curved hair follicles.^{19,20}

Following each thermolysis treatment session, hair regrows in 20–40% of treated follicles.

The blend method—a combination of both electrolysis and thermolysis—subjects the hair follicle to both chemical and thermal destruction through the use of galvanic and low-intensity high-frequency currents, respectively. Although the combination treatment is slower, it is significantly more effective and less painful than the individual use of each method.^{18,19}

While pain tolerance to electrolysis has been shown to develop over several sessions,²⁰ the use of topical anesthetics can decrease treatment pain significantly. Correct needle placement is relatively painless; however, premature or delayed activation of the electrode during its insertion or withdrawal may cause pain as well as damage to the superficial skin, which could lead to scarring.²¹ Electrolysis is more effective on anagen hairs; therefore shaving within a few days before electrolysis greatly increases its efficacy because it ensures that only growing anagen hairs are epilated.²⁰ This is particularly important during the initial treatment of an area because as many as 60% of the hairs may be in telogen, which are difficult to eradicate permanently. Hair regrowth rates following treatment are highly variable and range from 15–50%. The wide variation has been attributed to the differences in equipment used and to the skill of the operator. Multiple treatment sessions are necessary because of the practice of avoiding simultaneous treatment of adjacent hair follicles (within 3–4 mm of each other) in order to reduce unnecessary thermal skin injury. As many as 100 hairs can be removed in 20 minutes with thermolysis.

Infectious diseases potentially transmissible through electrolysis include bacterial and viral infections such as impetigo, verrucae, molluscum contagiosum, and herpes simplex (HSV).^{5,22} As such, the area of skin to be treated should be completely examined and clear of bacterial and viral infections prior to treatment in order to avoid autoinoculation.⁵ For patients at known risk of HSV reactivation, prophylactic oral antiherpetics should be considered for upper lip or chin treatment. While relatively rare, other contagious skin diseases such as leprosy, syphilis, tuberculosis, acquired immune deficiency syndrome, and hepatitis can also be spread from one patient to another through electrolysis.⁵ Cutaneous sporotrichosis has also been reported on the anterior neck of a patient after electrolysis in the same area.²³ Electrolysis needles must be of either the prepackaged sterile disposable type or sterilized with the steam autoclave, chemiclave, or dry heat and stored to ensure sterility prior to use. The use of unsterilized and/or reusable electrolysis needles could lead to these infections and, thus, are contraindicated.^{5,20}

Underlying medical conditions should be taken into consideration in patients undergoing electrolysis, including a history of bacterial endocarditis, heart valve surgery or anomalies, and presence of cardiac pacemakers or joint prostheses. Antibiotic prophylaxis in patients at high risk

for the development of bacterial endocarditis as well as in patients with prosthetic devices should be considered.^{24,25} Short bursts of electric current (< 5 seconds) are generally safe in patients with cardiac pacemakers; however, as a precaution, peripheral pulse or cardiac monitoring is suggested. True galvanism is considered safe in the presence of cardiac pacemakers and is most often used by nonmedical personnel.^{5,21}

Patients who are prone to hypertrophic scarring, keloids, postinflammatory hyperpigmentation, or other cutaneous dyschromias should be advised that these complications may result from electrolysis treatment. Of particular risk are scar-prone areas of the face such as the mandible and upper lip⁵. Pigment tattooing has also been described as a complication of electrolysis.^{26,27} Other drawbacks include the discomfort, cost, and extensive time necessary for each treatment session.²⁸

Autoelectrolysis is a heavily advertised method of home electrolysis that usually involves the use of a galvanic device. It has been declared unsafe by the British Medical Association and has been noted to be unsatisfactory because of its difficulty of use and associated treatment pain and scarring.²⁹

Recently, an over-the-counter device for personal use has been developed to thermally remove unwanted hair.³⁰ The hand-held self-treatment device (no!no! Thermicon™, Radiancy Inc, Orangeburg, NJ) uses the principle of thermal transference to heat the hair shaft through a thermodynamic wire. This device is purported to remove unwanted hair from all parts of the body excluding the face, ears, neck, and genitalia.

Lasers

The FDA approved the first hair removal laser system in 1995. Laser-assisted hair removal can be used to treat large areas of unwanted excess hair with fewer complications and less discomfort than electrolysis or thermolysis.²¹ Improved clinical results are ascribed to the laser's ability to specifically target pigment-containing hair when an appropriate wavelength, pulse energy and duration are selected. Laser treatment is targeted to the bulb and bulge of the anagen hair follicle, each of which absorb red or infrared wavelengths. The pulse duration (or exposure time of the laser light on the skin) is matched to the thermal relaxation time of these targets so that adequate (but not over) heating of the unwanted hair is achieved. The epidermis has a short thermal relaxation time of up to 7 ms while the hair follicle has a much longer thermal relaxation time of 40–100 milliseconds (ms). Shaving the hair-bearing site is performed preoperatively in order to prevent conduction of thermal energy to the adjacent epidermis from overlying hairs. Additional unwanted epidermal heating is prevented by application of a cooling gel, spray, or air device concomitant with laser energy delivery. Epidermal cooling also minimizes treatment discomfort as does application of

topical anesthetic creams. Pneumatic skin flattening (PSF), whereby the skin is pulled taut during laser irradiation, has also been shown to decrease laser-associated discomfort.³¹ The use of PSF for pain control is based on the gate theory of pain transmission, as the process involves activation of tactile and pressure skin receptors to block transmission of pain to the brain during laser activation.

The energy density necessary to coagulate a hair follicle is dependent on the color, diameter, and depth of the hair shaft. The hair follicle can be selectively targeted by light absorbed by an endogenous component of the follicle, such as melanin or keratohyalin, followed by thermal necrosis limited to the follicular zone. Hair shafts of lighter color and smaller diameters require the use of higher energy densities or an exogenous material or chromophore that will be absorbed by the hair or placed in the follicular orifice to absorb the light.²¹ The latter technique is exemplified by the SoftLight process which uses a Q-switched neodymium:yttrium-aluminum-garnet (QS Nd:YAG) laser

to target a topically applied carbon-based solution that has presumably penetrated the hair follicle.³² The carbon particles within the follicle absorb the light and undergo a rapid temperature increase. The thermal energy results in selective injury to the germinative cells of the follicle that are in contact with the solution. The shock wave produced by increasing temperature causes mechanical damage to the hair follicle, which delays hair regrowth. Topical application of carbon solution has not been proven to be redundant more effective than using the pigment-specific lasers alone, particularly in patients with dark terminal hairs.³³ Melanin-encapsulated liposomes have also been used with limited success in laser-assisted removal of blonde and white hair.³⁴

The systems that have been used for selective hair removal include ruby (694 nm), alexandrite (755 nm), diode (800 nm) and Nd:YAG (1064 nm) lasers with relatively long pulses (millisecond pulse durations). (Table 39-2). A 2- to 6-month growth delay is typically observed

TABLE 39-2—Hair Removal Lasers and Light Sources

LASER AND LIGHT SOURCES	Wavelength (nm)	Pulse duration
Long-pulsed ruby lasers	694	1-3 ms
Chromos™ 694 (SLS Biophile, Ltd, Carmarthenshire, UK)		
EpiLaser™ (Palomar Medical Technologies, Inc., Burlington, MA, USA)		
EpiTouch™ Ruby (ESC Sharplan, Norwood, MA, USA)		
Palomar E2000™ (Palomar Medical Technologies, Inc., Burlington, MA, USA)		
Long-pulsed alexandrite lasers	755	2-20 ms
Apogee 5500™ (Cynosure, Inc., Westford, MA, USA)		
Arion™ (WaveLight Technologies AG, Germany)		
GentleLASE® (Candela Corp., Wayland, MA, USA)		
UltraWave™ Alexandrite (Adept Medical Concepts, Rancho Santa Margarita, CA, USA)		
Diode lasers	800-810	5-400 ms
Comet™ (Syneron Medical Ltd, Yokneam, Israel)	810 nm diode + RF	
F1 Diode Laser™ (Opusmed Inc., Montreal, Quebec, Canada)		
HR-Force (Alderm, N.A., LLC, Irvine, CA, USA)		
Lumenis One LightSheer™ (Lumenis Inc., Santa Clara, CA, USA)		
MeDioStar™ (Asclepion Laser Technologies, Jena, Germany)		
Sonata™ (Orion Lasers, Fort Lauderdale, FL, USA)		
VariLite™ (Iridex corp., Mountain View, CA, USA)	532 nm KTP + 940 nm diode	
Q-switched Nd:YAG lasers	1064	5-20 ns
MedLite® IV (ConBio, Dublin, CA, USA)		
MedLite® C6 or RevLite™ (HOYA ConBio™ Medical & Dental Lasers, Fremont, CA, USA)	532 nm + 1064 nm	
SoftLight™ (Thermolase, San Diego, CA, USA)		
Long-pulsed Nd:YAG lasers	1064	5-250 ms
Apogee Elite™ (Cynosure, Inc., Westford, MA, USA)	755 nm alexandrite + 1064 nm Nd:YAG	
Athos™ (Quantel Médical, France)		
ClearScan™ (Sciton Inc., Palo Alto, CA, USA)		

(Continued)

TABLE 39-2—Hair Removal Lasers and Light Sources (Continued)

LASER AND LIGHT SOURCES	Wavelength (nm)	Pulse duration
CoolTouch VARIA™ (CoolTouch Inc, Roseville, CA, USA)		
CoolGlide® CV, Excel or Vantage® (Cutera Inc., Brisbane, CA, USA)		
Dualis ^{VP} (Fotona Medical, Slovenia)	532 nm KTP+1064 nm	
Dualis ^{XP} or Fidelis ^{XP} (Fotona Medical, Slovenia)		
FriendlyLight® Nd:YAG (Aerolase™, Tarrytown, NY, USA)		
Gemini ⁱ ™ (Laserscope, San Jose, CA, USA)	532 nm KTP +1064 nm	
GentleYAG® (Candela Corp, Wayland, MA, USA)		
Lyra-i™ or XP™ (Laserscope, San Jose, CA, USA)		
Lumenis One Multi-Spot™ Nd:YAG (Lumenis Inc., Santa Clara, CA, USA)		
Mydon™ (WaveLight Technologies AG, Germany)		
Profile MP™ 1064 Module (Sciton Inc., Palo Alto, CA, USA)		
Smartepil IITM (Cynosure, Inc., Westford, MA, USA)		
UltraWave™ II, III (Adept Medical Concepts, Rancho Santa Margarita, CA, USA)	755 nm alexandrite + 1064 nm	
Intense pulsed light (IPL)	590-1400	2.5-5 ms
Aurora DS™ (Syneron Medical Ltd, Yokneam, Israel)		
Clareon HR™ (Novalis Medical, Tampa, FL, USA)		
Cynergy III™ (Cynosure, Inc., Westford, MA, USA)	595 nm pulsed dye, 1064 nm Nd:YAG + 500-950 nm pulsed light	
EpiCool Platinum-HR™ (OptoGenesis™, Austin, TX, USA)		
EpiLight™ (ESC Medical, Yokneam, Israel)		
EsteLux™ (Palomar Medical Technologies, Inc., Burlington, MA, USA)		
Galaxy DS™ (Syneron Medical Ltd, Yokneam, Israel)		
Lumenis One Universal IPL Module™ (Lumenis Inc., Santa Clara, CA, USA)		
MediLux™ (Palomar Medical Technologies, Inc., Burlington, MA, USA)		
McCue™ Variable Pulsed Light System (Adept Medical Concepts, Rancho Santa Margarita, CA, USA)		
McCue Ultra VPL™ (McCue Corp, Inc., Belton, MO, USA)		
Novalight™ or Omnilight™ FPL (American Medical Bio Care, Inc., Newport Beach, CA, USA)		
Profile MP™ or BBL™ (Sciton Inc., Palo Alto, CA, USA)		
Quadra Q4™ Platinum Series (DermaMed USA, Inc., Lenni, PA, USA)		
SkinStation™ (Radiancy, Inc., Orangeburg, NY, USA)		
Silk'n SensEpil™ (Home Skinovations, Ltd, Israel)		
Solarus HR™ (Novalis Medical, Tampa, FL, USA)		
Solis™ (Laserscope, San Jose, CA, USA)		
SpectraPulse™ (Adept Medical Concepts, Rancho Santa Margarita, CA, USA)		
StarLux™ (Palomar Medical Technologies, Inc., Burlington, MA, USA)	1064 nm Nd:YAG + 500-670 nm/870-1400 nm pulsed light	
Pulsed light and heat energy (LHE)	430-1100 nm	35 ms
SpaTouch™ or SkinStation™ (Radiancy, Orangeburg, NY, USA)		
IPL + Bipolar radiofrequency (RF)	680-980 nm + RF	200 ms
eLight DS™ (Syneron Medical Ltd, Yokneam, Israel)		
Variable Pulsed Light (VPL)	530-950 nm	7-385 ms
Energist ULTRA™ (Energist Ltd., Swansea, UK)		

after a single laser treatment. A meta-analysis of hair removal laser trials from 1998 to 2003 documented hair reductions of 52.8, 54.7, 57.5, and 42.3% for the ruby, alexandrite, diode, and Nd:YAG lasers, respectively, at least 6 months after the final of three laser treatments.³⁴ Observed hair regrowth after laser-assisted hair removal is sparse and individual hairs are thinner and paler in color. Incomplete elimination and hair regrowth are presumably caused by incomplete follicular destruction. Multiple treatment sessions are timed so that the unwanted hairs are in the anagen phase which may further reduce hair regrowth. Minimal edema and transient erythema may be evident in the treated areas for the first 24–48 hours post-treatment.

A drawback to using shorter wavelengths (e.g., 694 nm ruby) is that a more deeply pigmented epidermis impedes light penetration of the dermis with a subsequent decreased effect on germinal cells. In addition, unwanted epidermal injury may occur, resulting in hypopigmentation. The ideal treatment candidate for laser-assisted hair removal should have untanned, pale skin (phototypes I-II) and dark hair. Patients with darker skin tones (Fitzpatrick skin phototypes IV– VI) should only receive treatment with the alexandrite, diode or the Nd:YAG lasers, which safely deliver longer wavelengths and avoid unwanted postoperative skin dyspigmentation.^{35–37} The Nd:YAG laser with its longer wavelength is the safest type to treat darker skin tones, but the alexandrite and diode lasers are more effective because their shorter wavelengths are more greatly absorbed by melanin in the hair shaft and follicle.

Side effects are minimal in a majority of cases. When present, they include mild discomfort, transient erythema, perifollicular edema, purpura, skin dyspigmentation, crusting, vesicular formation, folliculitis or pseudofolliculitis, and rarely, erosions, scarring, reticulate erythema and urticaria vasculitis.^{38–41} A topical corticosteroid may help minimize the duration of these side effects. The direct insertion optical method, which delivers laser energy directly to the hair bulb through an optical needle, has also been successful in preventing these complications in a pilot study.⁴² The incidence of pigmentary alteration and vesication increases in patients with tanned skin or intrinsically darker skin phototypes.

One notable side effect of laser-assisted hair removal is the stimulation of new hair growth within previously irradiated areas or in close proximity to the treatment regions.^{43,44} This “paradoxical effect” has been reported after treatment with each of the laser and light hair removal systems. Its development has been attributed to activation of dormant hair follicles by either the application of subthreshold fluences or the conduction of heat to surrounding areas which eventuates in synchronization of the hair growth cycle. Pili bigemini, the extrusion of two hairs from the same follicular opening, has been reported following sublethal damage to hair follicles.⁴⁵ Higher energy may enable complete destruction of the hair

follicles as long as consideration is given to the skin type and an effective epidermal cooling system.

Acneiform lesions have been described following laser hair removal with a predilection in younger patients, those treated with the Nd:YAG laser and Fitzpatrick skin type V.⁴⁶ The severity of the reaction is usually mild and lasts only for a short duration. A significant increase in sebum excretion occurs 4 to 12 months after laser hair removal even though there is a reduction in sebum gland size. This may be attributed to decreased resistance to sebum outflow following absence of the hair shaft.⁴⁷ Hyperhidrosis, bromhidrosis, and leukotrichia have also been documented in 11, 4, and 2% of patients, respectively, after laser-assisted axillary hair removal.⁴⁸

Non-Laser Light Sources

Noncoherent light sources with a spectrum of wavelengths ranging from red/yellow (590 nm) to infrared (1200 nm) can be used to deposit optical energy along the length of the hair shaft. Similar clinical responses to those outlined with the long-pulsed laser systems have been reported with a significant reduction in hair after a series of intense pulsed light (IPL) treatment sessions.⁴⁹ A lower energy IPL system has even been introduced for at-home hair removal with slightly diminished (but still adequate) clinical hair reduction.⁵⁰

Other variations of IPL technology have included pulsed light and heat energy (LHE) systems which have also demonstrated clinical hair reduction.^{51,52} The addition of bipolar radiofrequency (RF) to IPL treatment enables lower levels of optical energy to be applied with good clinical effect, fewer side effects, and the potential to be used across a wider range of skin types.⁵³ A bipolar RF device has two electrodes through which current passes and travels at a fixed distance to provide a tissue penetration depth of 4 mm. Optical and RF energies are produced as high as 30 J/cm² and 25 J/cm³, respectively, with pulse durations up to 200 ms. While RF devices are not used to affect hair removal alone, the synergistic combination with IPL may improve the efficacy of optical energy delivery and produce effective epilation of even blond and white hair phenotypes.⁵⁴

Variable pulsed light (VPL) can also affect long-term removal of unwanted hair with minimal and transient side effects.⁵⁵ The VPL system creates output wavelengths from 610 to 950 nm and delivers a pulse train of filtered visible light, in which each train contains up to 15 micropulses.

Side effects of IPL therapy include vesication, erosions, crusting, leukotrichia, folliculitis, paradoxical hypertrichosis, and postinflammatory hyperpigmentation.⁵⁶ Second-degree skin burns on the bilateral upper arms have also been reported, presumably from the use of excessive energies.⁵⁷

TABLE 39-3— Comparison of Hair Removal Methods

Methods	Advantages	Disadvantages
Temporary		
Bleaching	Fast, inexpensive, widely available	Unsuitable for dark skin, irritation /allergy possible to persulfate/peroxide
Trimming	Safe, widely available, good for children	Impractical for large areas
Shaving	Fast, wide available, inexpensive	Rough stubble, irritation, folliculitis possible
Tweezing	Good for small areas	Slow, painful, impractical for large areas
Waxing	Fast, good for large areas	Painful, thermal burns/folliculitis possible
Mechanical Epilation	Fast, inexpensive, widely available	Skin irritation/folliculitis possible
Chemical Depilatories	Inexpensive, widely available	Irritation possible, not suitable for thick hair (beards)
Surgery	N/A	Expensive, scarring possible
Radiation Therapy	N/A	Carcinogenic, impractical
Permanent		
Electrolysis/Thermolysis	Moderate price, good for small areas and all skin colors	Painful, operator-dependent, infections/dyspigmentation/scarring possible
Lasers/Light Sources	Expensive, good for all skin types, most clinically effective	Expensive, limited to dark hair, professional expertise required
Photodynamic Therapy	Highly effective, may be useful for light hair	Expensive, slower process due to ALA incubation

Photodynamic Therapy

Photodynamic therapy (PDT) with topical application of aminolevulinic acid (ALA) followed by red light exposure has also been used for the destruction of excess or unwanted hair.⁵⁸ ALA induces the follicular synthesis of the potent photosensitizer, protoporphyrin IX.⁵⁹ Prior to treatment, hair is first wax-epilated and then an ALA-containing solution is applied to the skin surface. Over several hours, the ALA is more selectively absorbed in the hair follicles than in the epidermis. The treatment site is then exposed to red light that activates the photosensitizer, causing cell membrane damage from the creation of singlet oxygen. A 40% decrease in hair regrowth has been reported 6 months after a single treatment.^{58,59} Using PDT, it is possible to treat large areas independent of skin or hair color. Because the method is still in the developmental stage, further studies are needed to determine its long-term safety and efficacy.

SUMMARY

The presence of excessive hair can be a source of distress that can lead to anxiety, depression, and a reduced quality of life in affected individuals. Current nonmedical methods of hair removal include shaving, waxing, depilatories, electrolysis, and laser and light-based devices (Table 39-3). Unfortunately, no single treatment method can achieve complete hair eradication in every skin and hair type.

Lasers and light sources can be used for expedient treatment of large areas of skin with minimal discomfort and lead to a prolonged delay in hair regrowth. In addition,

the selectivity and therefore effectiveness of these methods are less operator-dependent than other modes of therapy. The noninvasive and needless technology greatly reduces the risk of disease transmission and scarring. Darker skin phototypes are more prone to side effects which can be minimized by utilizing lasers with longer wavelengths. Combined treatments are becoming more popular and trials are underway to determine if the delivery of multiple wavelengths with or without topical medication improves clinical outcomes. Additional studies are needed to assess the appropriate number and timing of treatment sessions in order to obtain even longer and, perhaps, permanent hair removal.

What We Know: Laser-Assisted Hair Removal

- Multiple lasers and light sources (including alexandrite, diode, and Nd:YAG) are available to remove hair
- Prolonged/permanent hair reduction (50-80%) is typical after a series of 3 to 5 monthly treatments
- All skin phototypes can be safely treated, but greater safety margin of Nd:YAG laser in darkest skin tones
- Most effective for elimination of dark (brown or black) hair
- Minimal side effects are observed with proper device use
- Professional delivery of treatment is advised to rule out medical contraindications and to prevent untoward side effects

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Tattoo Removal

40

Uwe Wollina, M.D., and Christa De Cuyper, M.D.

INTRODUCTION

Tattoos are marks on the skin made by inserting pigment. This can occur either be by accident (accidental or traumatic tattoos) or by intention as a part of culture, fashion, or individual expression and less frequently as a medical procedure.^{1,2} The latter can be professional or nonprofessional that will have an impact on possible options for their removal. Amateur tattoos are less dense, placed at variable depths, and composed of carbon-based ink. Professional tattoos contain a variety of densely packed, colored pigments at a uniform depth. Most tattoo colorants are industrial pigments, and chemical industries have never produced them for human use, but only to stain consumer goods. Once implanted, the ink particles are phagocytosed by resident dermal fibroblasts, where they permanently remain in the superficial dermis.

Tattoos have become a common a part of fashion and body art. Tattooing is associated with risk-taking activities. In a representative US-survey in the age of 18 to 50 years, 24% had tattoos. Tattooing was equally common in both sexes, but body piercing was more common among women. Other associations were a lack of religious affiliation, extended jail time, previous drinking, and recreational drug use.³

The National Longitudinal Survey of Adolescent Health Public Use Dataset, which provides a nationally representative sample of 6072 adolescents collected in 1995 and 1996, has been evaluated for tattoos. Of the total sample of youths, 4.5% reported having permanent tattoos. Tattooing was significantly associated substance use, violent behaviors, and school problems.⁴

A study among US undergraduate students enrolled 454 students. The prevalence of body piercing was 51%, and that of tattooing was 23%. There was no significant difference in the prevalence of tattooing by sex. Male athletes were more likely to be tattooed than male nonathletes. No relationships were shown between piercing/tattooing and age or measures of body somatotype.⁵

In a recent study from Germany, the total prevalence of tattooing was 8.5 %. In the age between 14 and 44 years 15 % are tattooed. Unemployment and lack of partnership correlate positively with body modifications. Tattooing

correlates with the perception of reduced mental health and both, tattooing and body piercing correlate highly with increased "Sensation-Seeking" behavior.⁶

In Australia, a random sample survey of individuals aged 14 years and over had been performed, collected between June and September 1998 (n = 10,030). The results show that 10% have had a tattoo at some point in their lives. Men are more likely than women to report tattooing, while females are more likely to report body and ear piercing. The prevalence of tattooing and body piercing is considerably higher among injecting drug users.⁷

In a study that examined autopsy records from the New Mexico Office of the Medical Investigator from 2002 to 2005, a total of 3430 individuals (1666 white Hispanics; 1764 white non-Hispanics), aged 18 to 100 years, with homicidal or accidental manners of death were investigated for tattoos. Results indicate statistically significant differences in tattoo frequencies by ethnicity (52% Hispanic vs. 29.5% non-Hispanic), sex (46.8% men vs. 25.9% women) and age cohort. Hispanics were more likely to have multiple tattoos than non-Hispanics (41% and 19%, respectively), and were 4.67 times more likely to have a religious tattoo, and 7.13 times more likely to have a gang tattoo than non-Hispanics. Significant patterns in language of text tattoos and correlations with manner of death were also noted.⁸

MOTIVES OF TATTOO REMOVAL

Studies suggest that at least 50% of individuals later regret their tattoo.⁹ The motives for tattoo removal are manifold from improved self-esteem to increased credibility. Some individuals want removal because of the tattoo design or improper performance or because of religious reasons.^{10,11}

In a US-study of 2006, more women than men were asking for tattoo removal compared to 1996. The women were white, single, college educated, and between the ages of 24 and 39 years; they reported being risk takers, having stable family relationships, and moderate to strong religious beliefs. Commonly, tattoos were obtained at approximately 20 years of age, providing internal expectations of uniqueness and self-identity. In both the 1996 and the 2006

studies, a shift in identity occurred, and removal centered on dissociating from the past.¹²

PRE-TREATMENT MEASURES

Patients seeking advice for tattoo removal need information about the available techniques and their benefits and limits. A realistic expectation of the patient is necessary. In general, tattoo removal is a time-consuming procedure and more expensive than tattooing. It is very helpful if the patient can provide detailed information about the inks used. This should be rounded up by manufacturer's material safety leaflets. Since inks are often mixed by the tattooist, this information remains mostly incomplete.

A small area should be treated first to evaluate tolerability and skin reaction to treatment. Photographs should be taken before and during therapy. A signed patient's information and consent is mandatory.

Since tattooing bears a higher risk of transmissible disease like hepatitis B, tuberculosis or HIV infection, both doctor and nurse should take preventive measure to avoid infection. Females during gravidity and lactation should not be treated.

TECHNIQUES OF TATTOO REMOVAL

Lasers

The use of lasers has been effective in the removal of some but not all tattoos (Table 40-2). Q-switched lasers have been found to be safe and effective in the treatment of tattoos. Q-switching allows the production of laser pulses with extremely high peak power. In all such Q-switched lasers, the risk of scarring is less than 4.5% with proper use.¹³

The precise mechanisms of tattoo lightening are still largely unknown, but it appears that laser therapy leads to instant alteration of optic properties of the tattoo pigments, partly by destruction and partly by thermal, photochemical (cleavage of pigment molecules by laser irradiation and oxidation), or photoacoustic (fracturing molecules by virtue of acoustic or pressure waves) reactions.¹⁴



Histologic and electron microscopic analyses of biopsies have shown the disintegration of pigments into smaller fragments which were then phagocytosed by macrophages or carried away via the lymphatic system. There are also detectable structural changes in the pigment particles. About 4 weeks after treatment, pigment released from the cells can be observed intracellularly which may contribute to lightening.^{15,16} The response to laser treatment can vary greatly because of the wide range of tattoo ink. Previous in vitro quantitative chemical analysis of tattoo pigments found that the most common elements were aluminium, titanium, and carbon. Titanium overrepresentation was identified as the main reason for a poor response to laser treatment. Picosecond (ps) lasers were found to be more effective in achieving a greater degree of clearing than nanosecond (ns) lasers.¹⁷

For most tattoos a series of laser applications is necessary to achieve a sufficient level of pigment lightening. In between the treatments and for sometimes after the last procedure, sun protection and avoidance of tanning beds is highly recommended to prevent hyper- or hypopigmentations at the laser-treated sites.¹³

Ablative Lasers

Ablative lasers have been used for laser-assisted dermabrasion in traumatic (accidental) tattoos (Figure 40-1). In a study with four patients with traumatic tattoos in the face, a variable pulsed erbium:YAG laser was employed. The fluence of the ablative pulses was 5 J/cm². The endpoint for the treatment was the macroscopic removal of the foreign bodies. Postoperatively, silver sulphadiazine, or polyvinylpyrrolidone was applied daily until wound closure occurred. Use of a total sun block was mandatory for a period of 6 months. Pre and postoperative photographs were taken of all cases. The results were evaluated by a panel of four independent observers, who were asked to judge the percentage of tattoo clearance as well as any evidence of pigmentation problems or scarring. All results were rated from good to excellent. In all patients, a nearly complete clearance of the traumatic tattoo was achieved in one laser session. No scarring, skin atrophy, or hypo or hyperpigmentation was observed. Furthermore, a high patient satisfaction rate was achieved. Compared to mechanical

FIGURE 40-1 Ablative erbium-YAG laser treatment of an accidental tattoo. Before (A) and after (B) three treatments (3 mm spot size, 1000 J, 10 Hz). There is a marked improvement of discoloration but slight telangiectasias have been developed.

dermabrasion, the procedure is more reliable and causes fewer side effects.^{18,19} Mafong et al. (2003) used a pulsed CO₂-laser for removal of a cosmetic lip-liner tattoo.

Non-Ablative Lasers

In order to selectively remove tattoo pigments placed in the dermis, pulsed lasers must meet the following criteria:

1. The laser wavelength must be well absorbed by the targeted ink.
2. The heat generated should be spatially confined to the target.
3. The energy delivered must be sufficient to cause the desired effects.²⁰

The basic principles of the theory of selective photothermolysis imply that the wavelength used for tattoo removal should match the absorption spectra of the tattoo pigment and that the pulse duration should be less than the thermal relaxation time of the target.²¹ Consistent with this theory, the current standard of treatment for tattoo removal rests with the use of Q-switched lasers with nanosecond pulse durations and wavelengths of 755 nm (Alexandrite) for black, blue and green tattoos and 1,064 nm (neodymium [Nd]:YAG) for blue and black tattoos; 694 nm (ruby) for blue, black, and green tattoos; and 532 nm (Nd:YAG) for red tattoos.²² (Table 40-1).

TABLE 40-1—Suitability of Various Q-switched Laser Types for Tattoo Dyes

Color	(694nm)	(1064nm)	(532nm)	(755nm)
Black	+	+	-	+
Blue	+	+	-	+
Green	+	-	-	+
Red	-	-	+	-
Yellow	-	-	(+)	-

Q-switched lasers enable the deposit of energy very quickly, thereby producing an additional “photoacoustic” effect. The intense heat transients cause some particles to shatter and kill the cells in which the pigment resides. The rupture of pigment-containing cells eventually triggers phagocytosis and the packaging of tattoo fragments for lymphatic drainage.^{23,24}

Q-SWITCHED RUBY LASER (694NM)

Ruby lasers operate with a wavelength of 694 nm, pulse times of < 40 ns (usually 25 ns), and fluences up to 8–10 J/cm². Black, blue-black, and dark blue dyes are most responsive while the results are mixed for green and blue dyes. Red, orange, and light blue dyes respond poorly.²⁵ The Q-switched ruby laser is effective for the removal of black, blue, and green inks. The laser penetrates to a depth

TABLE 40-2—Laser Tattoo Removal—An Overview

Author(s)	n	Laser type (tattoos)	Wavelength (nm)	Spot size (mm)	Fluence (J/cm ²)	Pulse width (ns)	Outcome
Levine & Geronemus (1995)	48	QSNdYAG*	1064/532	2	10-14/5-7	5-10	better effect of 532 nm vs. 1064 nm
Ferguson & August (1996)	148	QSNdYAG	1064/532	2/1.5	10/2.5	10	>75% lightening after 1-11 treatments (black, blue and red)
Ross et al. (1998)	16	QSNdYAG	1064	1.4	0.65	35 ps	12/16 tattoos cleared better with ps pulses
		QSNdYAG	1064	2.5	8	10	than with ns pulses
Werner et al. (1999)	93	QSNdYAG	1064/532	2-6	12/5	10-20	13.2-18.6 treatments for lightening
Leuenberger et al. (1999)	42	QSNdYAG	1064	3	5-10	10-20	2nd best for black-blue tattoos
		QSRL**	694	5	4-10	25-40	best for black-blue tattoos
		QSAL***	755	3	6-8	50-100	least effective
Ho et al. (2006)	144	QSNdYAG	1064	3	3.6-4.8	6	107 tattoos achieved clearance >80%
Fitzpatrick & Goldman (1994)	25	QSAL	755	3	4-8	100	>95% clearance after 8.9 treatments (black & blue)
Alster (1995)	42	QSAL	755	3	4.75-8	100	4.6-8.5 treatments for complete clearance
Bukhari (2005)	20	QSAL	755	3	4-7.5	100	>75% clearance in 50% after 3 to 6 sessions

* QSNdYAG, Q-switched Nd:YAG laser; ** QSRL, Q-switched ruby laser; *** QSAL, Q-switched alexandrite laser.

of approximately 1 mm and has spot sizes up to 6.5 mm. Because this wavelength is well absorbed by melanin, caution should be used, as injury to melanocytes can lead to transient hypopigmentation and even depigmentation as well as textural change. The goal of treatment should be immediate tissue whitening (corresponding to water vapor in the skin) with minimal or no bleeding, and as with all laser treatments, no more than 10%–20% spot overlap should be employed. When compared to the other Q-switched lasers, the Q-switched ruby laser was shown to have the highest clearing rate after four and six treatments of blue-black tattoos. However, >95% clearance was only obtained in 38% of the tattoos.²⁶ For amateur tattoos, it has been reported that a mean of 4.92 treatments are needed to achieve clearance of >90% of pigment.²⁷ Other studies suggest only 11%–28% of professional tattoos achieve >75% clearance after more than six treatments.^{28,29} Schreibner et al.,³⁰ and colleagues compared treatment outcomes in 101 amateur and 62 professional tattoos. After an average of four sessions 87% of amateur, but only 11% of professional tattoos were at least 80% lighter. Lowe et al.,³² found different results with 10 J/cm². After 5 treatments, 22 of 28 professional tattoos were more than 75% lighter. Levins et al.,³¹ also reported similar results with excellent outcomes and minimal side effects. Kilmer and Anderson³⁴ have reported that black, blue-black, and green tattoos respond best to ruby laser treatment. Amateur tattoos required 4–6 sessions and professional tattoos usually 6–10, but sometimes more than 20. In general, it can be said that professional tattoos, tattoos on distal sites, and recent or deep tattoos require a greater number of sessions for removal.³³

Q-SWITCHED Nd:YAG LASERS (532 NM AND 1064 NM)

The Q-switched neodymium: yttrium aluminium garnet (Nd:YAG) laser emits infrared light with a wavelength of 1064 nm and a pulse duration of <20 ns. Systems are available with a spot size of up to 8 mm and energy densities up to 12 J/cm². A frequency-doubling crystal, in this case a potassium titanyl phosphate (KTP) crystal, cuts the wavelength in half to 532 nm, which is within the spectrum of visible light (green) and is primarily absorbed by red dyes and melanin. The repetition rate of up to 10 Hz and the larger beam diameter, now up to 8 mm at 1064 nm or 6 mm at 532 nm, allow rapid and effective treatment of close-together and deep tattoos. The Q-switched Nd:YAG laser system overcomes the obstacle of excessive melanin absorption and is used to remove blue and black ink and tattoos in darker skin types (1064 nm), or red pigment (532 nm). The clinical endpoint following laser treatment is whitening of the skin with occasional mild pinpoint bleeding. Current models offer a spot size range of 1.5–8 mm, which may be more appropriate for eyeliner tattoos. Generally, more than 75% of red pigment can be removed in 3 sessions.^{17,35,36}

The 532 nm wavelength (green light) is absorbed by hemoglobin, and as a result, purpura lasting 1 week to 10 days frequently occurs after treatment. This wavelength is also effective for red, orange, and occasionally yellow ink. In 63% of red tattoos, >75% clearance was achieved after one to five treatments at 2.5 J/cm². In this same study, only two of eight yellow tattoos faded.³⁵

Some reports have detailed the paradoxical darkening of red tattoo pigment as well as other skin-toned, yellow, and pink tattoos.^{37,38} It is seen quite often during laser removal of permanent make-up (De Cuyper 2008; Figure. 42-2). Brown may turn into orange and green/yellow (Jimenez et al. 2002). One reason for darkening is that the laser pulse reduces ink from rust-colored ferric oxide (Fe_2O_3) to jet black ferrous oxide (FeO).⁴¹ Similarly, bright colors may contain white ink made up of titanium dioxide (TiO_2 , Ti^{4+}) that is reduced to TiO_2 or blue Ti^{3+} upon laser treatment.

The long 1064 nm wavelength has the deepest penetration and carries the least risk of hypopigmentation; however, it is also the least effective in removing brightly colored pigments. Of all the laser systems, it is the one we recommend for use in darker skin types. This wavelength may also be useful when residual, more deeply placed ink particles are all that remain, as well as in the treatment of eyeliner tattoos, because it is less likely to damage the hair follicle.

Ferguson and August found that 79% of amateur black tattoos were >75% clear after one to five treatments at 1064 nm, and 74% of professional tattoos achieved similar clearance but required up to 11 treatments (average 6.3).³⁵

Q-SWITCHED ALEXANDRITE LASER (755 NM)

Although this laser system has the least amount of tissue splatter owing to its slightly longer pulse duration of approximately 50 ns - 100 ns (compared to 5–15 ns for the Nd:YAG and 15–40 ns for the ruby laser), and a density of 9 J/cm² it is not as successful as the other models. The effectiveness increases with energy density. On average, 4–10 sessions at intervals of 1–2 months are needed.^{42,43}

Similar to the Q-switched ruby laser, the alexandrite is most effective for removing black, blue, and green inks. As with the other lasers, the clinical endpoint is tissue whitening. In a study by Stafford, et al. an average of 11.6 treatments was required to completely remove professional blue-black tattoos, compared to 10.3 treatments for the same results in subjects with amateur tattoos. Hypopigmentation occurred in 80% of treated subjects, which resolved within 3–4 months of treatment.⁴⁴ In an uncontrolled study, removal of tribal tattoos in Arabic women of skin type III-IV was performed by using the Q-switched alexandrite laser. Twenty female subjects aged 35–50 years from similar racial and ethnic backgrounds with amateur tattoos were treated. Q-switched alexandrite laser with a fluence range 4.0–7.5 J/cm² (mean 6.05) was used at 6–12-week intervals. Total treatment numbers ranged from three to six sessions

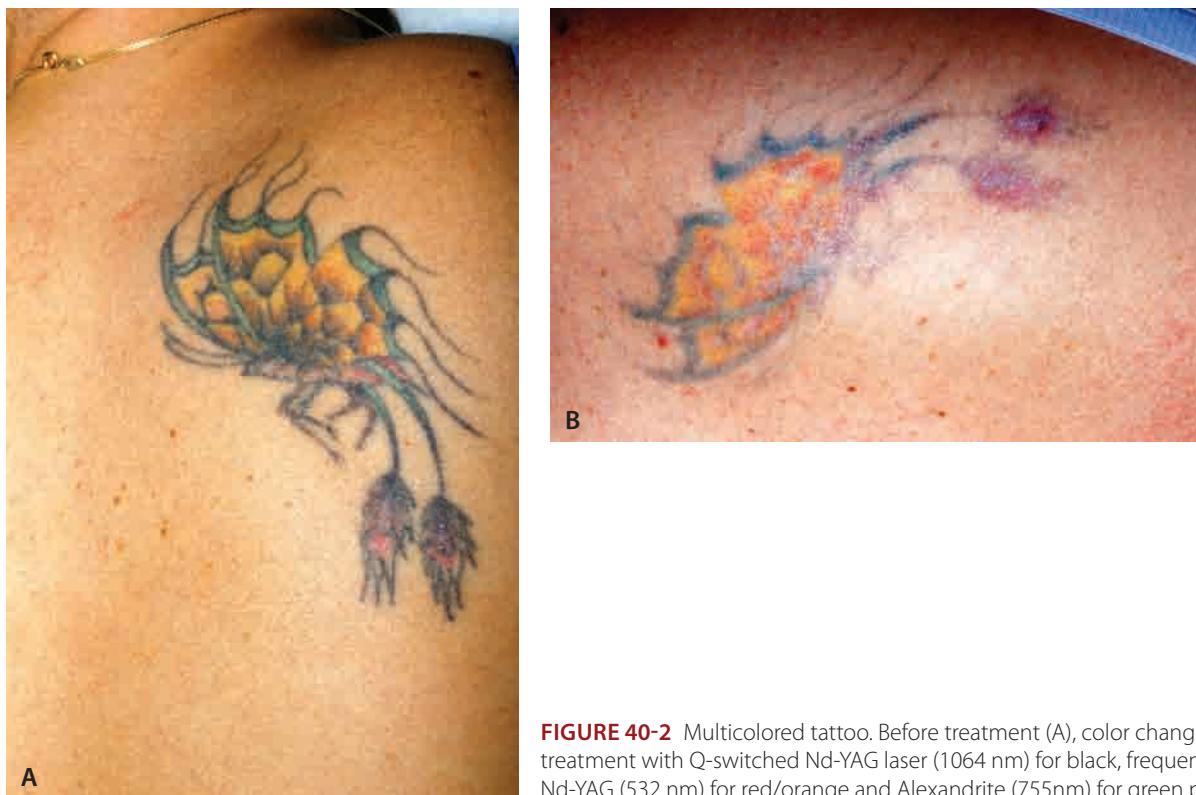


FIGURE 40-2 Multicolored tattoo. Before treatment (A), color changes during laser treatment with Q-switched Nd-YAG laser (1064 nm) for black, frequency-doubled Nd-YAG (532 nm) for red/orange and Alexandrite (755nm) for green pigments (B).

(mean 4.15) with single-pulse technique application. More than 95% lightening was achieved in five patients, after three to six sessions at fluence range of $6\text{--}7.5\text{ J/cm}^2$ and >75% lightening in 10 subjects, after three to six sessions of treatment at fluence range of $4\text{--}7.5\text{ J/cm}^2$. Pinpoint bleeding was observed in one case but no pigmentary alteration or scarring was seen. Tattoo pigment removal by Q-switched alexandrite laser is an effective method in skin type (III-IV) with minimal side effects, which gives high patient satisfaction.⁴⁵

Amalgam tattoos result from deposition of metallic particles (e.g., silver, mercury, copper, zinc, and tin) into the oral mucosa. Their clinical and histologic appearance is similar to that of decorative tattoos. An amalgam tattoo on the buccal mucosa and gingiva was treated with a Q-switched 755 nm alexandrite laser. Three treatments were delivered at 8-week time intervals (average fluence = 6.8 J/cm^2). Significant lightening of the tattoo was achieved after each of the three treatments without adverse sequelae.⁴⁶

Complications of Laser-Assisted Tattoo Removal and Their Management

Wenzel et al.⁴⁷ reported on 12 patients who received treatments with improper treatment parameters. In all patients, they diagnosed hypo- or hyperpigmentations and scar formation at the treatment site. In particular, the pulse

duration of the light sources or lasers applied were considerably longer than those required by the principles of selective photothermolysis. The light intensities of those devices are normally not sufficient to destroy the pigment particles. Instead of destruction, the pigment particles in the skin are heated up and the heat is conducted to the adjacent tissue causing unspecific tissue injury. Lasers or intense pulsed light sources with millisecond pulses and low light intensities are clearly not suitable to be applied for tattoo removal.

Multicolored professional tattoos require numerous sessions for complete removal, and it is not uncommon that some dye remains. Purple and yellow dyes appear to be particularly therapeutically challenging.⁴⁸ If pigment remains, often as irregular, lighter patches, or if it does not respond to laser therapy, treatment may be attempted with a combination of ablative laser and Q-switched laser. Remaining pigment located in deeper layers of the skin can be reached by the Q-switched laser after ablation of the surface tissue.

In rare instances, patients with tattoos containing metal salts—mercury (red), cadmium (yellow), chrome (green) and cobalt (blue)—may experience local allergic or photoallergic skin reactions or, very rarely, systemic reactions. Ashinoff et al.,⁴⁹ reported a woman who experienced an allergic reaction and whose tattoo was more than 75% lighter after only two sessions. It is conceivable that the profound inflammatory and immunologic reaction that developed after laser treatment helped lighten the tattoo. Two patients developed transient immunoreactivity that

presented as regional lymphadenopathy, after laser tattoo removal of professional black and blue-green tattoos. These reactions resolved without any complications.⁵⁰

Allergic reactions most often occur to red tattoo dye (Figure 40-3). These reactions are often not responding to topical or intralesional corticosteroids.⁵¹ In less inflamed cases, selective laser-assisted removal of red pigment, (e.g. with a Q-switched frequency-doubled Nd:YAG laser at 532 nm might be helpful), in other cases surgical excision might be the only option.^{52,53}

A case of an immediate urticarial reaction has been observed in a 26-year-old female after Q-switched Nd:YAG laser tattoo removal. The patient was treated with 3 days of prednisone, cetirizine, and ranitidine before subsequent laser treatments. Prophylactic treatment suppressed all subsequent reactions to laser therapy. Prophylactic treatment with steroids and antihistamines prevented reactions with subsequent laser treatments. Reactions after laser removal are rare, but may increase as popularity of skin art increases with the need for subsequent removal.⁵⁴

In recent times, industrially-manufactured organic pigments (mono- and di-azo dyes, polycyclic pigments of phthalocyanine, dioxazine, and quinacridone pigment classes) have been used instead of metal salts. Samples of 30 tattoo inks were examined using quantitative electron x-ray microanalysis. The technique reliably identifies all elements with the exception of those elements with atomic numbers less than 11.

In this study, professional inks were analyzed and compared with the material safety data sheets supplied by the tattoo ink manufacturers. Of the 30 tattoo inks studied, the most commonly identified elements were aluminum (87% of the pigments), oxygen (73% of the pigments), titanium (67% of the pigments), and carbon (67% of the pigments). The relative contribution of elements to the tattoo ink compositions was highly variable between different compounds. Overall, the manufacturer-supplied

data sheets were consistent with the elemental analysis, but there were important exceptions. The composition of elements in tattoo inks varies greatly, even among like-colored pigments. Knowledge of the chemical composition of popular tattoo inks might aid the clinician in effective laser removal.⁵⁵

Titanium—a constituent of blue tattoo ink, seems to be responsible for resistance to treatment with Q-switched Nd:YAG laser. In an animal study using rabbits, blue tattoos were unresponsive and quantitative energy dispersive spectrometry revealed a high amount of titanium in this particular ink.⁵⁶

Based on a recent analysis of tattoo pigments, two widely used azo compounds were irradiated in suspension with laser and subsequently analyzed by using quantitative high-performance liquid chromatography and mass spectrometry. The high laser intensities cleaved the azo compounds, leading to an increase of decomposition products such as 2-methyl-5-nitroaniline, 2,5-dichloraniline and 4-nitro-toluene, which are toxic or even carcinogenic compounds. Moreover, the results of the chemical analysis show that the tattoo colorants already contain such compounds before laser irradiation. Because of a high number of patients undergoing laser treatment of tattoos and based on the results of these findings in vitro, it would be an important goal to perform a risk assessment in humans regarding laser-induced decomposition products.⁵⁷ Although there is no data available that this happens in vivo, or that it is clinically relevant, findings are not yet conclusive.

The monoazo compound pigment yellow 74 (PY74; CI 11741) was found to be the major pigment in several of the tattoo inks. In vitro studies suggest that PY74 photodecomposes to multiple products. Three of the major photodecomposition products were identified by nuclear magnetic resonance and mass spectrometry as N-(2-methoxyphenyl)-3-oxobutanamide (*o*-acetoacetaniside), 2-(hydroxyimine)-N-(2-methoxyphenyl)-3-oxobutana-mide and N,N'-bis(2-methoxyphenyl)urea. These findings suggest that the use of PY74 in tattoo inks could potentially result in the formation of photolysis products, resulting in toxicity at the tattoo site after irradiation with sunlight or more intense light sources.⁵⁸ Newer dyes are also not “tissue inert,” but instead act as a chronic stimulus possibly leading to the development of reactive lymphoid hyperplasia (pseudolymphoma).¹³

The trauma caused by the placement of the dye can lead to a Köbner response or micro-scarring, visible after pigment removal as textural changes. Depending on energy density, wheals, punctate bleeding, blisters, and crusts may form following treatment. Textural changes usually resolve within 4–6 weeks; hence there should be a minimum of 4 weeks between sessions (Figure 40-4). Topical antiseptics may be used to prevent infection.¹³

A common side effect is the appearance of (usually transient) hypopigmentations, which occur in more than

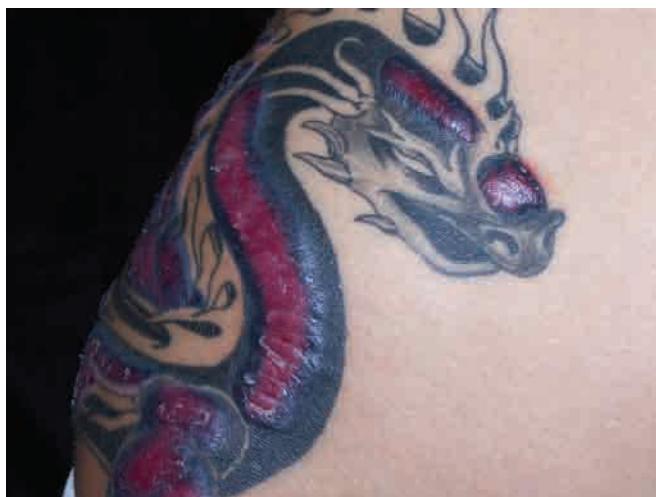


FIGURE 40-3 Allergic reaction to red tattoo dye in a multicolored professional tattoo.



FIGURE 40-4 Texture changes after multicoloured tattoo removal (A) before, (B) after treatment with Q-switched Nd-YAG laser (1064 nm) for black, frequency-doubled Nd-YAG (532 nm) for red/orange and Alexandrite (755nm) for green pigments.

38% of patients treated with Q-switched ruby lasers and typically remain for 2–6 months. The number of sessions is considered a risk factor in the development of hypopigmentations, (i.e., the greater the number of sessions the higher the risk of their developing). Pfirrmann¹³ reported approximately 10% of patients who develop permanent hypopigmentations. This side effect is observed much less often in Nd:YAG laser therapy because melanin absorbs less of the light in the emitted wavelength. This makes it especially suitable for darker or tanned skin.⁵⁹

In patients with persistent hypopigmentation, repigmentation using an excimer laser may be attempted. Hypopigmented skin developed following tattoo removal with the Q-switched Nd:YAG laser in patients. The hypopigmented area remained unchanged for more than 4 years, until the use of the 308-nm xenon-chloride excimer laser induced a significant repigmentation in 40 sessions more than 14 months. The excimer laser has the potential to influence the reduced activity of the melanocytes, as demonstrated with electron microscopy.⁶⁰

Hyperpigmentation tends to depend more on skin type than laser treatment. Lasting scarring or textural alterations (e.g., a puckered appearance resembling cigarette paper, mild erythema, or a waxy surface) can occur in rare instances.^{24,31} Hyperpigmentations usually depend on skin type. According to Fitzpatrick there is increased risk among patients with darker skin. Patients should avoid sun exposure or ensure adequate sun protection before and after treatment. Treatment may consist of hydroquinone and regular use of sun protection; fractional photothermolysis may be another option.^{61,62}

Permanent color changes from red, skin color, white, yellow, or brown tones to black, gray-black, or dark green

are not uncommon. Absorption spectra of common tattoo pigments and their reaction to irradiation at 532 and 752 nm have been evaluated in an in vitro study with samples of 28 tattoo pigments and India ink. The pigments were mixed in agar and analyzed with a spectrophotometer. These agar plates were irradiated with Q-switched wavelengths of 532 and 752 nm. The highest absorbance of red was in the complementary spectrum, while blue, yellow, and orange had peaks in the adjacent portion of the visible light spectrum. There is great variability in the absorbance of green tattoo material. In general, pigment darkening was more likely when treated with the 532-nm wavelength than with the 752-nm wavelength. Pigment darkening was noted at both wavelengths in all iron-containing pigments except black. It was variable in those containing titanium. Pigments tested responded with either clearance or darkening at 532 nm; however, response at 752 nm was more limited. This leads to the following conclusions: (1) Tattoo pigment absorption spectra can explain why some colors are more resistant to removal. (2) Pigment darkening is a complex process.⁶³

Tattoos can darken after laser treatment because of the reduction of ferric oxide to ferrous oxide. This can be rectified with repeated Q-switched laser treatment and the use of a resurfacing laser. Peach et al.⁶⁴ observed color changes in 33 of 184 (17.9%) multicolored tattoos. This effect is attributed to titanium dioxide, which is used as a lightener, and the reduction of iron-containing pigments to iron oxide. These usually respond to further laser treatments, but there is no guarantee. It is thus advisable to test an unnoticeable area for color changes as well as lightening associated with repeated treatment.⁴⁸

For textural alterations and scarring, possible treatments consist of erbium:YAG laser or pulsed carbon

dioxide laser as well as fractional photothermolysis.⁶⁵ A study by Ho et al.⁶⁶ used onion extract, heparin, allantoin gel (Contractubex® gel, Merz) prophylactically to prevent scarring. In the study, Contractubex® was applied to 61 tattoos while the comparison group of 58 tattoos did not receive any topical therapy. Twice daily application between laser treatments led to a significant reduction in the frequency of scarring.⁶⁵

An unusual reaction to laser removal has been observed in traumatic tattoos among three patients with dermal inclusions of gunpowder who were shot at close range. Treatment was tried in each patient with a Q-switched Nd:YAG laser at a medium fluence (4–6 J/cm²). But during treatment of our patients, each pulse provoked sparks and the immediate formation of bleeding transepidermal pits. After the healing process was completed, poxlike scars and the spreading of pigments in the skin around the initial points of the tattoo developed. The authors hypothesize that the rapid transfer of high-energy pulses to powder particles creates microexplosions of these fragments resulting in cavitation and provoking transepidermal holes and subsequent scars. This adverse effect was only produced if the tattoo resulted from gun powder being shot at a short distance from the skin.⁶⁷

Hair growth may be affected by laser removal. A 32-year-old skin phototype III male underwent 10 intense pulsed light (IPL; Photoderm PL, Lumenis, Yokneam, Israel) sessions to remove a multicolored (green, yellow, black, and red) nonprofessional tattoo situated in his back. In the 9th session, the appearance of lanugo hairs located in part of the treated area was noted. In the 10th session, the hair became thicker and was exactly located in the whole treated area.⁶⁸

Pain Management for Laser Therapy

Tattoo removal with a Q-switched laser is often a painful procedure. The sensation of pain associated with the treatment is immediate and acute.

Topical anesthetics are commonly used to make the treatment more comfortable. Although the use of topical anesthetics like EMLA-cream for alleviating the pain associated with cutaneous laser procedures, has been shown to be effective in several studies, most require a lengthy application time (1–2 hours) to be effective.⁷³

A multicentered, randomized, double-blind, placebo-controlled study has been performed using S-Caine Peel (ZARS, Inc (Salt Lake City, UT, USA). S-Caine Peel is composed of a 1:1 (w:w) eutectic mixture composed of lidocaine base 7%, USP, and tetracaine base 7%, USP. It is applied as a cream, dries on exposure to air, and forms a flexible membrane, which can be easily peeled off. Thirty adult patients undergoing laser-assisted tattoo removal were enrolled. Each subject received both the S-Caine Peel and placebo simultaneously for 60 minutes. The

primary efficacy parameter was a 100 mm visual analog scale (VAS) for patient self-assessment of pain. Mean VAS scores were 42 mm for the S-Caine Peel and 66 mm for placebo treatment sites ($p=.001$). Patients received adequate pain relief in 50% of S-Caine Peel sites versus 7% of placebo sites ($p=.002$). One occurrence of moderate to severe erythema was noted at both an S-Caine Peel and a placebo treatment site on removal of the S-Caine Peel after 60 minutes, which self-resolved quickly. Other side effects were limited to local mild, transient erythema at the application sites. Administration of the S-Caine Peel for 60 minutes prior to laser-assisted tattoo removal, was effective in significantly reducing pain levels associated with the procedure.⁷⁴

Application of topical anesthesia to the treated area of the skin is time-consuming, with moderate pain relief. Therefore new options have been evaluated to control the pain during treatment. Pneumatic skin-flattening (PSF) technology utilizes an evacuation chamber that generates skin compression and activates tactile neural receptors in the skin, resulting in afferent inhibition of pain transmission in the dorsal horn ('gate theory'). Eleven patients aged 17–25 years old who were treated for tattoo removal were enrolled in a pilot study. The patients were treated by a Q-switched Nd:YAG laser. Acute pain evaluation was performed on all 11 patients: one to two sites per patient with PSF, and one to two control sites without PSF. The study was limited by the fact that patients knew they were being treated with a device that might reduce pain. This may have influenced the outcome. The evaluation was based on a pain score. A lower pain score with PSF was observed in all but one patient (10/11 or 91%). The average reduction of pain is by two levels: from very painful to very mild pain. The energy transmission of the PSF window is 95%, resulting in essentially identical efficacy of the PSF treatment and the regular non-PSF treatment. This pilot study indicates that PSF technology may reduce pain in tattoo removal with medium energy density Q-switched lasers (3–5 J/cm²).⁷⁵

Alternative and Adjunctive Procedures

Surgery

Complete excision is only possible for smaller tattoos. Larger areas can be removed by shave-excision with healing by second intention (Figure 40-5). A bloodless field can ensure a complete removal of dermal pigment and reduce the operation time.⁷⁷ The wound can be covered with polyurethane dressings or dermal overgrafting.^{76,78}

A small study has been performed to evaluate precise, thin, tangential excisions of professional tattoos. Five healthy white males had their professionally placed tattoos excised at a depth of 0.2 mm using a Brown dermatome. Pre and posttreatment biopsies were used to measure the depth of

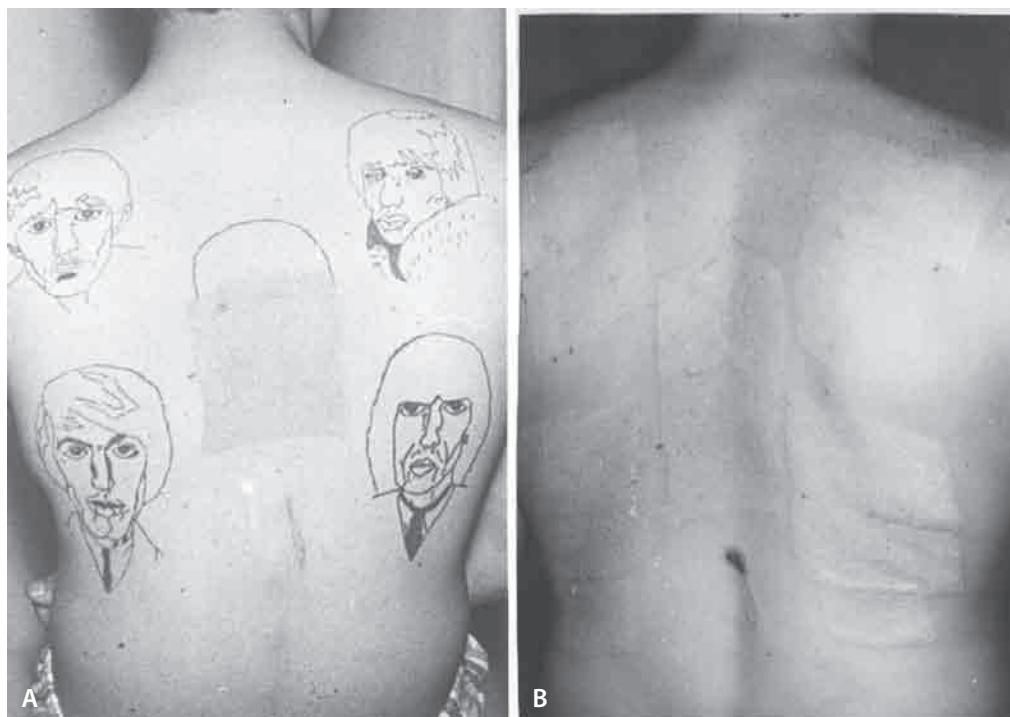


FIGURE 40-5 Tattoo removal by shave excision (From: Wollina U, Köstler E. Tattoos: surgical removal. *Clin Dermatol*. 2007;25:393–7).

the tattoo pigment. At 3 months posttreatment, four patients had no significant scarring and three patients retained only scattered flecks of tattoo pigment. Each patient demonstrated migration of the deeper dermal pigment to a more superficial level.⁷⁹ A superficial, tangential excision of a professional tattoo by a dermatome is a viable, low-risk, inexpensive procedure as long as the pigment lies superficially.

A method of tattoo removal in which the enzymatically (disperse) separated epidermis of an excised tattoo was grafted *in situ* was applied to three patients. Unlike the conventional skin-grafting procedure, this method resulted in the complete obliteration of the tattoos without donor site scars. The thinning of the tattooed skin using a Paget's-type dermatome before its exposure to an enzymatic solution facilitated the enzyme's infiltration of the basal layer of the epidermis. Hence, the time taken for the epidermis to separate from the tattooed skin was shortened.⁸⁰

Larger tattoos may need a sequential excision. Suture tension can be minimized using placation with presuturing, dynamic skin suture, or tissue expansion.⁸¹ Dermabrasion generally produces excellent results in the removal of congenital or acquired nonesthetic skin changes. Superficial traumatic (accidental) tattoos should be removed immediately after the accident. Dermabrasion is a useful method. Decorative tattoos can be successfully removed by repeated surface dermabrasion. In case of granuloma formation in traumatic tattoos, however, dermabrasion will not produce satisfactory results.⁶⁹

Salabrasion is the use of abrasion with table salt and a moist gauze pad to achieve a mixture of mechanical and chemical deep peeling.

In an open trial, 22 patients have been treated with a 3-minut salabrasion, once for repeatedly, on skin areas around 41 tattoos. In tattoos performed by laymen on forearm, upper arm or posterior, a single salabrasion produced acceptable to good results in the removal of tattoos. Frequently, single or repeated salabrasion resulted in hypopigmentation of the interfollicular epidermis with a more or less intensive skin-colored to brownish pigmentation of the follicle regions. The general impression of hyperpigmentation only occurred occasionally after single salabrasion and was independent of location. Single or repeated salabrasion resulted in an emphasis of the surface structure and increased wrinkling of the skin in due course, but not scar formation.⁷⁰

In a study in the UK, 33 patients, some with multiple tattoos were treated by salabrasion. In 14 patients with 28 tattoos only tiny flecks of pigment remaining visible; eleven showed a fair response, (i.e., the tattoo, although much lighter in color, was still legible but the patient was satisfied with the result); three showed a poor response, (i.e., the tattoo appeared as if untreated); four (two patients) defaulted. In general, as could be expected, the darker the tattoo the more difficult was its removal and those on fingers were particularly resistant.⁷¹

To reduce the risk of scarring, the salt should be removed completely after finishing the procedure, (i.e. by irrigation).⁹

Chemical Clearing Agents

In guinea pig studies on tattoo removal, glycerol was used as a clearing agent. Intradermal injection of clearing agents

induced dermal clearing but resulted in necrosis and scar. Transdermal application of clearing agents resulted in moderate reversible clearing, which was localized to the superficial layers of the skin and did not result in complications. Temporary clearing of superficial skin layers may be performed in an apparently safe and reliable manner. Clearing should lead to increased penetration of laser light to tattoos and should, therefore, increase treatment efficiency. Further study is needed to determine the degree to which this change is of clinical value.⁷²

Several cream removal systems have been introduced to the market. These consist of chemicals that penetrate the skin and gradually digest the tattoo pigment. Among these are Tattoo-Off (BeauPlexa, Sarasota, FL), which claims to contain only natural botanicals such as aloe leaf juice, lemon extract, orange peel, rosemary and sage leaves, and calendula flower extract in conjunction with hydroquinone, salicylic acid, and a variety of preservatives. The manufacturer claims that dramatic results are seen after 7 months of daily application. Another topical cream is Tat B Gone (Sandy Springs, GA), whose Website does not disclose the ingredients in the product.⁸² The Rejuvi Tattoo Remover solution (Rejuvi Lab, South San Francisco/CA) contains cosmetic deionized water, zinc oxide, magnesium oxide, calcium oxide, isopropanol, triethanolamine, and benzoic acid. The composition is said to have low skin toxicity and antiseptic efficacy. The Rejuvi Tattoo Remover is inserted into the dermis by a coil tattoo gun or a cosmetic rotary machine after topical anesthesia. It has claimed that this product is capable of mobilizing tattoo pigments from the skin and forms a scab with tattoo pigments on the treated skin area, which then peels off in 10–20 days. It is recommended to perform the treatment on a tattoo area not greater than 15 cm² in order to control the discomfort level after treatment. If needed, a second treatment should be performed on the same area after sufficient skin healing (usually about 3 months).

Cheng⁸⁶ reported that Rejuvi Tattoo Removal has been found to be non-color-selective (it removes all tattoo pigments). In the initial study with 98 patients, the success rate was 100% for removal of cosmetic facial tattoos (tattooed eyebrows) and 92% for body tattoos. The scarring rate was zero for cosmetic facial tattoos and 6% for body tattoos. No pigmentary change was found for either type of tattoo.⁸⁵ There has been no study found from another group using this chemical mixture.

A 27-year-old Latino man with a 24 × 10 cm tattoo on his right lower leg had received 7 treatments using Rejuvi Tattoo Removal at weekly intervals. He subsequently developed hypertrophic scars in the area treated using Rejuvi Tattoo Removal. He had no personal or family history of hypertrophic or keloid scars.⁸²

Veysey and Downs reported two patients who developed hypertrophic and hypopigmented scars, after treatment with Rejuvi Tattoo Removal on the forearms.⁸⁷ More recently, a patient experienced full-thickness skin loss requiring grafting after just one treatment on the lower leg.⁸⁸

Topical Imiquimod

Imiquimod is an immune-response modifier for topical use. It has been shown that topical application of 5% imiquimod cream to acute phase tattoos results in successful removal in an animal model, although fibrosis and loss of dermal appendages also occurred.⁸⁹ Less frequent application of topical imiquimod over a longer treatment period in the same animal model resulted in tattoo fading and fibrosis, without appendageal loss.⁹⁰

In a recent study, 14 albino guinea pigs were tattooed with black ink, and then randomly assigned into two groups: one underwent sequential laser treatments with a Q-switched alexandrite laser in conjunction with triweekly applications of 5% imiquimod cream, while the other group underwent laser therapy alone. Subjects were evaluated with clinical photographs and skin biopsies after six laser treatment sessions. The combination laser and imiquimod-treated group was clinically and histologically rated as having less pigment than the tattoos that were treated with laser alone ($p=.012$ and $p=.047$, respectively). Adjuvant imiquimod treatment had greater inflammation ($p=.002$) and fibrosis ($p=.002$) on post-treatment skin biopsies. The authors concluded that imiquimod appears to be a useful adjuvant to experimental laser tattoo removal in guinea pigs.⁹¹

Human experience seems to be different. Twenty subjects with two similar tattoos were enrolled in a randomized, prospective, double-blinded, case-controlled study. Tattoos were treated with either imiquimod or placebo daily and laser therapy every 4 to 6 weeks for a total of six sessions. The primary efficacy parameter was tattoo clearance (5-point scale, poor through complete). Secondary efficacy parameters included textural changes (5-point scale, minimal through severe), pain during and between laser procedures, and undesirable pigment alterations. Nineteen subjects completed the study. The mean score for tattoo clearance with imiquimod versus placebo was 3.2 versus 2.9 and, for textural changes, was 1.37 versus 1.21 (differences not statistically significant). There was no difference in subjective pain during and between laser sessions and no undesirable pigment alterations were reported. Adverse reactions were more frequent with imiquimod compared to placebo. Based on this study, the authors come to the conclusion that topical imiquimod is an ineffective adjunct to laser-assisted tattoo removal.⁹²

Magnets

To improve the clinical outcome, more recent developments have included the external application of magnets to improve the removal of magnetite skin tattoos after Q-switched laser treatment. The extraction of magnetite ($\text{Fe}_3(\text{O}_4)$) ink tattoos by a magnetic field was investigated, with and without Q-switched laser treatment. Magnetite particles (1.4 μm) were used to make mature, black skin

tattoos on hairless albino rats. A Q-switched ruby laser - fluence 3.5 J/cm^2 , 6.5 mm spot size, 40 ns pulse width was used for treatment. Permanent magnets (1.4 T, 6 mm diameter) were tested to extract the magnetite particles, alone and after laser light application. A magnetic field applied immediately after laser treatment extracted some ink when epidermal injury was present, and caused significant redistribution of magnetite into the upper dermis with vertical banding along magnetic field lines. When applied for 3 weeks following Q-switched ruby laser, magnets caused darkening of tattoos.⁹³ Magnetically-extractable tattoos may be feasible.

CONCLUSIONS

Tattoo removal has been studied in many trials, some randomized controlled but most uncontrolled. The best evidence is available for Q-switched laser treatment that allows in most tattoos a significant lightning that is color-dependent. The most challenging colors are white and yellow. The best results are obtained in black, blue and red tattoos. The composition of the pigment dyes needs to match with the wavelength of the laser to obtain an optimal result.

In contrast to Q-switched lasers, IPL is not recommendable because of long pulses and increased risk of scarring by tissue heating.

Surgical procedures are available from simple abrasive therapies (salabrasion, dermabrasion) to complex procedures using tissue expansion techniques, flaps, and grafts. In many parts of this World, simple procedures are often used as an alternative to lasers because of cost issues. Sometimes surgery is the only option to deal with a prolonged inflammatory response to tattoo dyes. No comparative randomized trials are available for surgical procedures.

Chemical clearing agents seem to offer a soft effect not depending on tattoo colors. A single study suggested efficacy, but more studies are needed. The technique has been used as an adjunct to laser treatment. In some patients chemical clearing agents can cause scarring.

Topical imiquimod cream has shown efficacy as an adjunct to laser treatment in animal models but published experience in humans is disappointing.

Consumer safety may increase if regulations for tattoo dyes would ban the use of harmful substances. New dye developments like microencapsulation of ink could be used to allow a complete and safe removal on demand.⁹⁴

What We Know

- Tattoos are skin marks that may contain a variety colored pigments. The removal of tattoos is not as easy as the tattooing itself, although this might be an art. *In general tattoo removal is a time-consuming procedure and more expensive than tattooing.*
- In tattoo removal laser is the treatment of choice in many cases. Q-switched lasers have been found to be safe and effective in the treatment of tattoos with a low risk of scarring. Q-switched lasers with nanosecond pulse durations and wavelengths of 755 nm (Alexandrite) and 1,064 nm (neodymium [Nd]:YAG) are effective for blue and black tattoos; 694 nm (ruby) for blue, black, and green tattoos; and 532 nm (Nd:YAG) for red tattoos. Ablative lasers like pulsed erbium:YAG or pulsed CO₂ have been used for laser-assisted dermabrasion in

traumatic (accidental) tattoos. In contrast to Q-switched lasers IPL is not recommendable due to long pulses and increased risk of scarring by tissue heating.

- Complete excision is only possible for smaller tattoos. Larger areas can be removed by shave-excision with healing by second intention. Larger tattoos may need a sequential excision. Suture tension can be minimized using placation with pre-suturing, dynamic skin suture, or tissue expansion.
- Dermabrasion is a cheap and useful method but the cosmetic outcome often is not as good as with lasers. Several cream removal systems have been introduced to the market that should gradually digest the tattoo pigment but multicenter randomized controlled trials are missing.

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Treatment of Photodamage

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INTRODUCTION

Photodamage refers to the complex progressive process of chronic ultraviolet radiation (UVR) exposure of the skin and its effects on skin aging and photocarcinogenesis. Indeed ultraviolet light is the primary external factor contributing to age-associated changes in the skin including wrinkling, dyspigmentation (hyperpigmentation and hypopigmentation), atrophy, and telangiectasias. The perceptions of both age and beauty are largely dependent on the appearance of the skin, which can be dramatically altered by chronic sun exposure. Thus, patients are increasingly seeking interventions to reduce or eliminate the signs of photodamaged skin.¹

The aging process of the skin is related to both genetic (intrinsic) and environmental (extrinsic) biologic mechanisms. Intrinsic aging is believed to occur because of DNA damage and telomere shortening. DNA damage, in addition to an inability to repair this damage, leads to cellular senescence. In addition, the telomeres at the end of chromosomes get progressively shorter with each cell cycle. Eventually a critical point is reached leading to cell signaling for apoptosis, or programmed cell death, suggesting a defined and finite life for cell functionality. Our expanding knowledge of external skin aging is centered around the effect of ultraviolet light on the skin, including direct DNA damage, the production of reactive oxygen species, and chronic inflammation.² In addition to ultraviolet radiation, smoking, poor nutrition, and excessive alcohol consumption are other extrinsic factors that contribute to skin aging. The two mechanisms, intrinsic and extrinsic, likely share a final common pathway as ultraviolet radiation has been shown to damage telomeres and induce cellular apoptosis through reactive oxygen species.³

At a cellular level, photodamaged skin is characterized by several changes within the epidermis and dermis of the skin. Within the epidermis, keratinocytes may show atypia and loss of polarity in addition to a general increase in the thickness of the epidermis of chronically sun-exposed skin. Within the dermis, fibroblasts are more numerous and hyperplastic, collagen I and III are decreased, and abnormal elastin accumulates. In addition, photodamaged skin shows signs of chronic inflammation, including mast

cells, macrophages, and T cells on histologic examination. This combination of cellular changes leads to the clinical appearance of photodamaged skin.²

The Ultraviolet Light Spectrum

The ultraviolet light spectrum is subdivided into several categories based on wavelength and biologic behavior. The skin represents the body's primary barrier to ultraviolet radiation, as UVR does not penetrate any deeper than the epidermis or dermis, depending on the wavelength. Ultraviolet A (UVA, 320 nm to 400 nm) accounts for approximately 95% of all the sun's ultraviolet radiation that reaches the earth's surface. Its longer wavelength readily reaches the dermis and is believed to play a significant role in both photoaging and immediate pigment darkening. Compared to photoaging, which take years of cumulative sun exposure, immediate pigment darkening occurs during and immediately after ultraviolet radiation exposure and fades rapidly, usually over a number of hours. It is a result of alteration of preexisting melanin within melanocytes.⁴

Ultraviolet B (UVB, 290 nm to 320 nm) is mostly filtered by the earth's atmosphere. However, some does reach the earth's surface, albeit in much smaller quantities than UVA. UVB has a shorter wavelength than UVA, and hence is primarily absorbed in the epidermis and contributes to the induction of cutaneous malignancies as well as delayed pigment darkening. The induction of cutaneous malignancies occurs through a complex interplay of angiogenesis, DNA damage, and formation of mutations, and failure of native repair mechanisms. Delayed pigment darkening occurs days after ultraviolet radiation exposure and is a result of increased activity of melanocytes including an increase in the number of melanocytes and increased melanin synthesis. Ultraviolet C (UVC, 200 nm to 290 nm) is undetectable at the earth's surface as it is absorbed by the earth's atmosphere entirely.⁴

Clinical Effects of Photodamage

Chronic ultraviolet radiation induces common clinical changes in the skin including wrinkling, dyspigmentation,

atrophy, telangiectasias, and the induction of cutaneous malignancies. Sun-induced wrinkling involves a combination of changes within the dermis of the skin including collagen, elastin, and the extracellular matrix (ECM). Collagen production is greatly reduced in photodamaged skin through a complex interaction of fibroblasts, ultraviolet radiation, and damaged collagen. Activator Protein 1 (AP-1) and Transforming Growth Factor B (TGF-B) are thought to play a primary role in the down regulation of collagen synthesis in photodamaged skin. In contrast to decreased levels of collagen, the production of elastin increases with subsequent exposure to ultraviolet radiation. However, the elastic fibrils are abnormal and accumulate within the dermis leading to solar elastosis and laxity of the skin. Lastly, changes within the extracellular matrix mediated through the upregulation of matrix metalloproteinases lead to collagen degradation and the breakdown of the ECM.⁵⁻⁶

As discussed earlier, sun exposure can lead to both immediate pigments darkening (primarily through UVA) as well as delayed tanning (primarily through UVB). In addition, changes in pigment such as lentigines, ephelides, poikiloderma of Civatte, and idiopathic guttate hypomelanosis can be seen in photodamaged skin. Although the mechanism is not completely understood, an interaction between ultraviolet radiation, melanocytes, and chronic inflammation is thought to mediate these changes.⁵⁻⁶

Studies have documented the effects of ultraviolet radiation and the induction of telangiectasias. Through upregulation of factors such as vascular endothelial growth factor (VEGF) and platelet derived endothelial growth factor (PDGF) and the downregulation of inhibitors such as thrombospondin-1 (TSP-1), UVR promotes local angiogenesis of the skin. In addition, this increase in cutaneous vascularity is thought to play a role in supporting the growth of cutaneous neoplasms.⁵⁻⁶ Cutaneous malignancies are beyond the scope of this chapter and are discussed elsewhere in the book.

EPIDEMIOLOGY

Changes in the skin from chronic ultraviolet radiation exposure affect both men and women equally, as well as all races. Patients with lighter skin types, with a tendency to burn easily, living in areas with more cumulative sun exposure, and with occupations requiring more outdoor exposure are at greater risk for photodamage to the skin. Women may seem disproportionately affected by chronic photodamage, but this is a reflection of medical-seeking behavior, especially for tertiary interventions to reduce or reverse photoaging.⁷ In 2002 alone, over 5 million nonsurgical and 1.5 million surgical procedures were performed costing over 13 billion dollars in order to improve the appearance of photodamaged skin.⁸

ETIOLOGY AND DIAGNOSIS

Ultraviolet radiation is considered the primary etiologic factor in photodamaged skin. Biologically, ultraviolet A (UVA) penetrates into the dermis and induces many of the changes of chronic photodamage. However, ultraviolet light should be considered on a spectrum with contributions from ultraviolet B (UVB) as well. Through its effects on DNA damage, the production of reactive oxygen species (ROS) and promotion of a chronic inflammatory state, ultraviolet radiation can accelerate the cutaneous aging process as well as induce cutaneous malignancies.^{2,5,6,9}

The diagnosis of photodamaged skin is made clinically as skin exposed to chronic ultraviolet radiation displays several characteristic features including fine and deep wrinkling, laxity, dyspigmentation, telangiectasias, variable thickness, and cutaneous malignancies. These clinical signs are most pronounced on areas of the body receiving the most sun exposure including the face, neck, dorsum of hands, and extensor forearms, and in persons with lighter skin types. Areas of the body that are "double-covered"- that is covered by two layers of clothing- such as the buttocks can often be used as comparison between photodamaged and photoprotected skin within an individual patient. Although not typically performed, the diagnosis of photodamaged skin can be confirmed by skin biopsy. Histopathologically, photodamaged skin displays several characteristic features including epidermal thickening, flattening of the dermoepidermal junction, disorganization of collagen, altered microvasculature, and solar elastosis.^{2,5,6,9}

OBJECTIVES

Over 1300 journal articles have been written on the subject of photodamage, along with countless book chapters. This work seeks to review recently published literature that provides strong evidence regarding effective prevention and treatment of photodamage.

Specifically, five research questions are posed:

1. How can photodamage be prevented?
2. What topical agents are effective in treating photodamage?
3. Are chemical peels effective in treating photodamage?
4. Are injectables and fillers effective in treating photodamage?
5. Are laser and light sources effective in treating photodamage?

These questions are answered through systematic PubMed searches, with the specific search criteria described in each section that follows.

PREVENTION

The sole etiologic agent that initiates the process of photodamage of the skin is the chronic exposure to ultraviolet

radiation. As such, reducing the amount of ultraviolet light one receives remains the cornerstone of the prevention of photodamage. Indeed, many visits to dermatologists involve a discussion regarding photoprotection, using sunscreens and photoprotective clothing. In addition, the medical community, the cosmetics industry, and various media outlets have each worked to educate the public about the importance of photoprotection. Although the emphasis of photoprotection has historically focused on blocking ultraviolet B, because of its contribution to skin cancer, a better appreciation of the effects of ultraviolet A on photoaging has led to “broad-spectrum” protective measures. Despite increased efforts at public education regarding photoprotection and advances in photoprotective technology, a segment of the population intentionally increases their exposure for a more “tanned” or “healthy” appearance.

Using the MEDLINE (PubMed) database to identify articles and abstracts relating to the prevention of photodamage, the term “Photoprotection” was used as a medical search heading (MeSH). Articles were limited to those written in English, published within the last 10 years, and that involve only human subjects. This search yielded 281 articles. Articles were hand searched and excluded if the articles did not deal with photoprotection as it relates to photodamage to the skin. For example, articles discussing photoprotection and vitamin D or photoprotection and the treatment of dermatologic disease were not included. In addition, reference lists of review articles were searched and studies included, when appropriate, as supporting evidence. For consideration for evidence, letters, case reports, case series, and basic science/animal studies were also excluded after reviewing individual articles. Fourteen articles were included as evidence for the utility of photoprotective clothing, sunscreens, and antioxidants for the prevention of photodamage.

Photoprotective Clothing

Photoprotective clothing and hats offer a convenient and effective means for the prevention of photodamage of the skin. In order to standardize and compare photoprotective abilities, the industry has adopted the ultraviolet protection factor (UPF) as a measurement standard. Many factors contribute to the UPF, including fabric materials, thickness of fabric, tightness of weave, as well as chemical treatments including UV absorbers and optical brightening agents. Photoprotective clothing offers the advantage of broad-spectrum UV protection and immediate and continuous effectiveness as compared to sunscreens where patients must apply the sunscreen a half hour before expected UV exposure and reapply thereafter.¹⁰

Despite claims of photoprotection, several recent studies have brought the issue of effectiveness into question. One study by Gambichler et al. examined 236 fabric

textiles from spring/summer clothing line collections during the period of 2000-2001 and tested their level of UPF. The authors discovered that a third of clothing products tested (78/236) provided poor protection from ultraviolet light (defined as UPF <15) and less than half (113/236) provided an UPF >30.¹¹ A review article by Hatch et al. summarized the current knowledge regarding sun protective clothing. Four separate studies conducted during the 1990s were reviewed in that article and found between 50-80% of summertime clothing delivered at least a SPF 15 photoprotective level.¹² In 2003 the European Committee for Standardization proposed guidelines for photoprotective clothing specifically marketed with UPF labeling. Photoprotective clothing must cover the area from the neck to the hip and at least three quarters of the upper arm, have a minimum UPF of 40, and have less than 5% UVA transmission.¹³

The evidence regarding the use of photoprotective clothing in the prevention of photodamage of the skin is mixed at best. Much of the conflicting evidence stems from the relative recent advent of clothing specifically marketed for photoprotection. The use of UPF as a measurement of photoprotection as well as higher standards for photoprotective clothing has led to more reliable clothing products for UV photoprotection. Biologically it makes sense that any product that blocks UVB and UVA from reaching the skin will prevent photodamage, however more studies are needed to elucidate the exact extent of such products.

Sunscreens

Sunscreens remain the most widely available and popular method for the prevention of photodamage of the skin. The oldest sunscreens utilize inorganic particles (physical blockers) such as titanium dioxide and zinc oxide to scatter and absorb ultraviolet radiation. Initially cosmetically displeasing because of the larger particle size and subsequent whitening appearance, newer products utilize nano- or micro-sized particles while maintaining broad-spectrum photoprotection. In contrast, newer sunscreens incorporate a variety of organic particles (chemical blockers) that absorb ultraviolet radiation and convert the energy into heat. Most current organic sunscreens combine both a UVB filter such as aminobenzoates, cinnamates, salicylates, and octocrylene with a UVA filter such as benzophenone, avobenzone, and ecamulse.¹⁰

The strongest evidence regarding sunscreens and photoprotection relates to the reduction of skin cancers. Sunscreens have been shown to reduce the number of actinic keratoses and squamous cell carcinomas in several studies.¹⁴⁻¹⁶ The evidence is not as strong in regards to basal cell carcinoma prevention, although several studies by Green et al. suggest a benefit.^{15,16} The role of sunscreens in the prevention of melanoma has been controversial with some studies actually suggesting an increased risk

of melanoma. A recent meta-analysis by Dennis et al. concluded that sunscreen use was safe and did not increase the risk of melanoma.¹⁷ Much of this discrepancy may be explained by earlier sunscreens offering little to no UVA photoprotection.¹⁸

An appreciation of the use of sunscreens in the prevention of photodamage of the skin is evidenced by the marketing of products, including daily moisturizers with sunscreens incorporated into the product itself. As discussed previously, many of the signs of photoaging including wrinkling, dyspigmentation, atrophy, and telangiectasias are brought on or accelerated by the chronic exposure of the skin to ultraviolet light. A study by Seite et al. demonstrated that daily sunscreen use could slow down the process of photoaging by preventing ultraviolet radiation from enacting its biologic effects on the epidermis and dermis.¹⁹

The evidence regarding the routine use of sunscreens in the prevention of photodamage of the skin is strongest for the prevention of cutaneous tumors including actinic keratoses and squamous cell carcinomas. The evidence behind the routine use of sunscreens in the prevention of basal cell carcinoma is not as strong, and the data regarding sunscreen and its relationship to melanoma is controversial. More research is needed in these areas. Finally, our knowledge regarding the effects of ultraviolet light, especially ultraviolet A, on photoaging provides indirect evidence supporting routine sunscreen use in the prevention of photoaging.

Antioxidants

Besides the direct damage caused by ultraviolet light on the DNA of cells within the epidermis and dermis, indirect damage through the production of reactive oxygen species (ROS) contributes to photodamage of the skin. Although the body has innate mechanisms to neutralize these reactive oxygen species, excess amounts can cause damage to the DNA, lipid membranes, and proteins within the skin. Antioxidants act by reducing and reversing the build-up of potentially harmful reactive oxygen species produced by ultraviolet radiation.

Although systemic antioxidants are commonly supplemented in diets, inadequate levels are delivered to the skin to produce any appreciable benefit. However, topical antioxidants such as vitamin C, vitamin E, green tea polyphenols, and other natural extracts work directly on the skin's surface. Special considerations regarding stability of the antioxidant, achievement of a biologically active concentration of the antioxidant, and formulating the antioxidant into an acceptable vehicle are all challenges in delivering antioxidants to the skin.

The evidence regarding the topical use of antioxidants in the prevention of photodamage of the skin should be considered within the realm of complementary and alternative medicine (CAM). Several studies by Jurkiewicz et al.

and Lin et al. have demonstrated the photoprotective ability of topical vitamin C and vitamin A within the skin.^{20,21} Other studies by Elmets et al. and Kim et al. have shown photoprotective effects through the topical application of green tea polyphenols.^{22,23} The additional benefit of topical antioxidants should be considered supplementary to other photoprotective measures such as sunscreens and protective clothing.

What We Know: Prevention of Photodamage

- Clothing can provide protection from ultraviolet light, though studies demonstrating a causal reduction in photodamaged skin are lacking
- Sunscreens have been demonstrated to reduce photoaging, actinic keratoses and squamous cell carcinomas
- Evidence regarding sunscreen use and decreased risk of basal cell carcinoma is not as strong
- The role of sunscreen in the prevention of melanoma has been a source of controversy, but it does not seem to increase the risk of melanoma
- Use of topical antioxidants are a reasonable additional step in sun protection, with sun avoidance, protective clothing and sunscreen being first-line approaches

TOPICAL THERAPIES

The topical treatments available for photodamaged skin are vast, with new treatment options becoming available continually (Table 41-1). It is the job of the physician to guide treatment based on the patient's degree of photodamage and the clinical evidence available, as well as the patient's preferences and expectations. Historically, topical retinoids have been shown to be the gold standard in the treatment of photodamaged skin,²⁴ however, many other topical agents are currently available. For those patients who are willing to comply with a daily treatment regimen and understand that results may take weeks to become clinically visible, topical therapies are a good option. However, in patients who want more immediate and obvious results, therapies such as botulinum toxin injections, fillers, chemical peels, and lasers may be used in addition to or instead of a topical regimen.

Because of the large number of topical treatments available, the goal of this review is to focus on the newest therapies currently available, those therapies that appear promising and are on the horizon, as well as older therapies that have good clinical evidence to support their use. A PubMed search was performed using the search criteria "photodamage treatment", limiting the search to human studies published in English within the past 5 years. This yielded 152 studies. Studies focusing on pathogenesis and

prevention of photodamage and laser and light treatments were excluded. Thirty-three articles remained for review. In addition, eight review articles discussing different topical therapies were reviewed. Of these, only those articles, which presented the highest level of evidence, were used. Results are summarized in Table 23-1.

Retinoids

Retinoids exert their effects by modulating gene transcription through the activation of the retinoid X receptor or the retinoic acid receptor.²⁵ Numerous randomized-controlled trials have been performed that show topical retinoids are effective at treating many of the signs of photodamage, namely fine wrinkles, lentigines, and tactile roughness. As a matter of fact, tretinoin 0.02% and 0.05%, as well as tazarotene 0.1% have been approved for the treatment of photodamage by the Food and Drug Administration.²⁵ Recently, other formulations of retinoic acid were tested in their efficacy for treating photodamaged skin. Weiss et al. conducted a randomized, double-blinded, placebo-controlled trial that evaluated the efficacy of 0.1% tretinoin microsphere gel.²⁶ The gel was applied once nightly for a total of 6 months. At completion of the study, statistically significant improvement was noted in fine wrinkling, mottled hyperpigmentation, yellowing/sallowness, and lentigines.

Retinol is another therapeutic option and is a cosmetic agent that is very similar to retinoic acid. Since skin keratinocytes are thought to metabolize retinol to retinoic acid, and since the latter have been shown to be effective for photodamaged skin, it has been hypothesized that retinol may be an effective treatment agent as well. Tucker-Samaras et al. completed an 8-week, double-blind, split face, randomized clinical study comparing a 0.1% retinol moisturizer against a vehicle, applied once daily.²⁷ At both 4-week follow-up and at completion of the study, significant improvement was noted in fine lines, wrinkles, pigmentation, elasticity, firmness, and overall photodamage, suggesting that this may be a viable treatment option. Although it is less irritating than retinoic acid and conveniently available over-the-counter, it is less effective than retinoic acid.

Topical Chemotherapeutics

Photodamage can lead not only to aesthetically displeasing features, such as wrinkles and lentigines, but can also cause precancerous lesions like actinic keratoses. There are many topical options available to treat actinic keratoses, including fluorouracil, imiquimod, and diclofenac. Fluorouracil, a topical chemotherapeutic cream, has been shown in multiple studies to be an effective treatment option for general photodamage as well. Sachs et al. examined the effects of topical fluorouracil on photodamaged skin both clinically and molecularly in a nonrandomized, open-label trial.²⁸ Patients were treated with fluorouracil

twice daily for a total of two weeks. Clinical improvement as well as an increase in the gene expression of keratin 16 (effector of epidermal injury), interleukin-1 beta (inflammatory marker), and matrix metalloproteinases 1 and 3 (extra cellular matrix degradation products) were noted. These results prove that topical fluorouracil causes epidermal injury, which stimulates wound healing and dermal remodeling, similar to that seen in the laser treatment of photodamage.

Combination Therapy

Leyden et al. performed a 24-week investigator-blinded randomized study that evaluated treatment of the decolletage area with a proprietary copper zinc malonate lotion and 4% hydroquinone applied twice daily, as well as tretinoin cream applied once daily.²⁹ Improvements were noted as early as 2 weeks, with tactile roughness improving first, followed by improvement in mottled hyperpigmentation, lentigines, wrinkling, and laxity. This study is particularly interesting because most of the therapeutic options available tend to focus on the treatment of photodamaged skin of the face, however patients often inquire about treatment of the decolletage area (neck and anterior chest) as well.

Lowe et al. compared the treatment outcomes of tazarotene 0.1% monotherapy versus tazarotene plus hydroquinone 4% in a randomized, double-blinded trial. Combination therapy proved to be more efficacious in the treatment of lentigines, mottled hyperpigmentation, and overall global improvement.³⁰

Combination therapies can also aim to decrease the side effects caused by the main treatment agent, and thus improve compliance and overall outcome. A double blind, placebo-controlled pilot study done by Jacobson et al. evaluated the effects of combining myristyl nicotinate (MN) with retinoic acid.³¹ Myristyl nicotinate is a lipophilic derivative of niacin that enhances skin barrier function and thus decreases the irritation that is often associated with retinoid use. Patients were treated with MN the month prior to initiating retinoid therapy. Once retinoids were begun, patients reported less side effects and easier tolerability.

A more tolerable and effective treatment for hyperpigmentation associated with photodamage involves the combination of 0.3% retinol with 4% hydroquinone. When compared to 0.05% tretinoin applied once daily, the combination regimen was as effective, if not more so effective, at treating hyperpigmentation, fine wrinkles, and roughness.³²

Growth Factors and Antioxidants

Growth factors are known to be involved in the mechanism of skin repair.³³ With this fact in mind, a multitude of topical growth factor preparations have been tried for the treatment of photodamaged skin. There have been numerous

clinical reports that show that these topicals may be effective in the treatment of photodamaged skin. A randomized, controlled, double-blinded study done by Mehta et al. studied the effects of a topical gel containing a mixture of over 110 growth factors, cytokines, and soluble matrix proteins in the treatment of facial photodamage, versus a vehicle gel applied twice daily.³⁴ After 3 months of therapy, a statistically significant reduction in fine lines and wrinkles were noted in the treatment group. Atkin et al. also conducted a similar trial in a 3 month, open-label, single center study using a serum containing multiple growth factors, cytokines, peptides, antioxidants, and depigmenting agents, and found a clinically significant reduction in fine and coarse wrinkles, along with improvements in skin texture, tone, and radiance.³⁵

Oresajo et al. observed the effects of a topical antioxidant mixture containing vitamin C, ferulic acid, and phloretin in a randomized-controlled clinical trial. Study participants applied the antioxidant preparation to one-half of the back and a vehicle control to the other. After exposing the patients to UV light, it was noted that the antioxidant-treated side had a higher minimal erythema dose, suggesting photoprotective effects of the antioxidant mixture.³⁶ Antioxidants alone are often marketed in over-the-counter skin care formulations. Due to their broad availability, they are further being explored for their effects on photodamage, wrinkles, and inflammation.³⁷

Other Therapies

There are a multitude of treatments available in the skin care industry that claim to improve the look of photodamaged skin; however only a few therapeutic agents actually have literature supporting their use. A single blinded study performed by Hussain et al. examined the effects of a manganese peptide complex applied twice daily for the treatment of photodamaged skin. At 12 weeks, both the individuals in the study and the blinded investigator noted

improvement in the signs of photodamage, most notably hyperpigmentation.³⁸

A randomized-controlled trial performed by Hsu et al. evaluated the effects of twice-daily application of a cream composed of green and white teas, mangosteen, and pomegranate extract. After 60 days, skin texture was improved, with notable reduction in pore size and roughness.³⁹

Wallo et al. performed a double-blind randomized-controlled trial that looked at the efficacy of a soy moisturizer for treating photodamaged skin. After 12 weeks of therapy, improvement was noted in mottled hyperpigmentation, blotchiness, dullness, fine lines, overall texture, skin tone, and overall appearance.⁴⁰

Future Trends

Niacin may have some role in future treatments of photodamaged skin. Niacin deficiency has been shown to cause photosensitivity in both animal models and human keratinocyte cell cultures, indicating that niacin may be involved in the pathway responsible for responding to UV damage.⁴¹ Further studies are needed to see its effect clinically.

Recently, the Liver X receptor (LXR) was found to be expressed in the skin and was considered to induce keratinocyte differentiation and improve epidermal barrier function.⁴² In vitro models have shown that targeting the LXR induces the expression of differentiation markers, ceramide biosynthesis enzymes, and lipid synthesis, therefore suggesting that LXR may be a novel target for developing therapies that target photodamage and skin aging.

Phosphocreatine is another potential therapy for photodamaged skin.⁴³ Retrospective reviews have revealed that phosphocreatine levels are elevated in burn victims and those with extensive skin necrolysis, and therefore is thought to aid in wound healing and skin remodeling. It has also been shown to protect the skin from UV damage. Given these findings, phosphocreatine may be a viable treatment option for photodamaged skin.

TABLE 41-1—Summary of Topical Treatments Reviewed

Drug	Dosage/Frequency	Level of Evidence	Strength of Recommendation
Rhytids and Lentigines			
Tretinoin (cream/gel)	0.02% and 0.05%/daily	1	A
Tretinoin micro sphere (gel)	0.1%/daily	1	B
Tazarotene (cream/gel)	0.1%/daily	1	A
Retinol moisturizer	0.1%/daily	1	A
Cytokine, growth factor, matrix protein gel	Unspecified/twice daily	1	B
Manganese peptide complex	Unspecified/twice daily	2	B

Drug	Dosage/Frequency	Level of Evidence	Strength of Recommendation
Combination Therapies:			
Copper Zinc malonate lotion	Twice daily	2	B
Hydroquinone cream Tretinoin cream	4%/twice daily Unspecified/daily		
Tazarotene cream Hydroquinone cream	0.1%/daily 4%/daily	1	B
Actinic keratoses			
Fluorouracil cream	5%/twice daily	2	A
Glycolic acid and fluorouracil	70% and 5%/weekly pulses	1	B
Jessner's solution and trichloroacetic acid peel	35%/one time	1	A
Overall texture and appearance			
Green and white tea, mangosteen, pomegranate extract	Unspecified/twice daily	1	B
Soy moisturizer	Unspecified/daily	1	B

What We Know: Topical Preparations

- Retinoids are the gold standard for topical treatment of photodamaged skin
- Retinols provide a less irritating but less effective alternative to retinoids
- Topical fluorouracil is effective in treating actinic keratoses and other manifestations of photodamage
- Topical preparations may effectively combine more than one active ingredient and usually include either a retinoid or retinol along with hydroquinone
- Growth factors have been shown to be effective in improving photodamage

obtained. Searches that are more specific were done using the search criteria “glycolic acid peels,” “Jessner’s solution peels,” “trichloracetic acid peels,” “salicylic acid peels,” “pyruvic acid peels,” and “phenol peels.” Studies that did not specifically address the changes associated with photodamage, such as acne and melasma treatment, were excluded. Only studies using the highest level of evidence to support the use of chemical peels in the treatment of photodamage were used.

Peeling agents are typically classified into very superficial, superficial, medium, and deep peels. The very superficial and superficial peels consist of the same peeling agents, with differing concentrations and treatment times based on the depth of peel desired. These agents include glycolic acid, lactic acid, lipohydroxy acid, pyruvic acid, resorcinol, salicylic acid, and Jessner’s solution (combination of lactic acid, salicylic acid, and resorcinol). Other combination peels are also commercially available. Trichloroacetic acid is the primary medium depth peeling agent. Deep peeling agents include Baker-Gordon phenol formula and phenol. The depth of chemical peeling can be judged by observing the change in color of the skin. The development of diffuse erythema in the treatment area indicates epidermal penetration. A white frost on the other hand indicates coagulative necrosis and thus penetration into the papillary dermis. A gray-white frost suggests that there is coagulative necrosis of the reticular dermis.⁴⁴ It should be noted that salicylic acid peels leave behind a white precipitate that is not the same as a true white frost. By having the ability to clinically observe treatment depths, the physician can easily tailor treatment based on each individual patient.

CHEMICAL PEELS

Chemical peels are another topical modality that helps to improve the appearance of photodamaged skin. There are numerous types of chemical peels available, each of which can help diminish the appearance of fine rhytids and lentigines. Depending on the depth of the pathology to be corrected and the type and concentration of peeling agent used, multiple treatments may be necessary to achieve the desired outcome, and treatment regimens are tailored to individual patients based on the depth of peel needed and their tolerance of the peeling agent.

In order to evaluate the efficacy of individual peeling agents, multiple PubMed searches were performed. Initially review articles discussing chemical peels were

Glycolic Acid

Glycolic acid peels have been used for years with successful outcomes in the treatment of photodamaged skin and other chronic conditions such as acne and melasma.

Glycolic acid is available in strengths ranging from 20-70% and different strengths are used depending on the condition being treated.⁴⁵ There are also numerous studies in the literature that support the use of glycolic acid peels as monotherapy and as a part of combination therapy for the treatment of photodamaged skin. Al Samahy et al. performed a histologic analysis of skin after treatment with a medium depth peel using 70% glycolic acid and 35% trichloroacetic acid. The study revealed decreased epidermal intracytoplasmic vacuoles, decreased elastic fibers, increased activated fibroblasts, and organized arrays of collagen fibrils.⁴⁶ These findings suggest that chemical peels, especially medium to deep peels, clinically and histologically can improve photodamaged skin through dermal remodeling. Kitzmiller et al. compared the effectiveness of multiple superficial peels using glycolic acid, versus one medium level peel with trichloroacetic acid, and showed that clinical outcomes are very similar; however, the superficial peels are better tolerated and often associated with less morbidity.⁴⁷

Recently, case reports have shown that patients with extensive histories of actinic keratoses and nonmelanoma skin cancer were successfully treated with 5-fluorouracil 0.5% cream in conjunction with glycolic acid peels.⁴⁸ A prospective, randomized-controlled study performed by Marrero et al. looked at the efficacy of 70% glycolic acid alone versus 70% glycolic acid and 5-fluorouracil (fluor-hydroxy therapy), applied in weekly pulse doses. This study also showed that actinic keratoses could be successfully treated with combination therapy. Patients were treated for 8 weeks total and post-treatment had a 92% clearance rate when combination therapy was used, in comparison to a 20% clearance rate when treated with glycolic acid alone.⁴⁹ In these cases, fluor-hydroxy pulse therapy offered a better clinical outcome by decreasing the morbidity associated with 5-fluorouracil monotherapy. The fluor-hydroxy pulse peel was also shown to be effective in the treatment of actinic porokeratosis.⁵⁰

Jessner's Solution

Jessner's solution is an alternative peeling treatment; however, upon review of the recent literature, it was noted to be most commonly referenced in combination with other agents. There are numerous studies that support the use of Jessner's solution in combination with varying strengths of trichloroacetic acid in order to achieve a medium depth peel. Combination therapy has been shown to be effective in the treatment of moderate rhytids and actinic keratoses.⁵¹ When compared with 5-fluorouracil monotherapy, combination therapy with Jessner's solution

and 35% trichloroacetic acid was found to be equally effective at treating actinic keratoses. Some patients preferred the one-time application of the chemical peel versus the twice daily application of 5-fluorouracil for several weeks. In noncompliant patients this may be an useful alternative treatment regimen.⁵²

Trichloroacetic Acid

Trichloroacetic acid peels can be used in concentrations up to 50% and can be used as either monotherapy or combination therapy. Techniques for use in monotherapy include the use of the Blue peel, which is a popular and widely utilized method.⁵³ The Blue peel allows the physician to more accurately control the depth of the peel achieved. By applying multiple coats of the Blue peel, and visually gauging the color changes with each coat, different treatment depths are achieved. A light blue color is suggestive of treatment in the papillary dermis, whereas a medium blue indicates treatment of the immediate upper reticular dermis. This allows for a more standardized approach to treatment, as trichloroacetic acid peels may be associated with higher morbidity when compared to other peeling agents.

Because trichloroacetic acid peels typically achieve a medium depth of peel, they are associated with longer healing times. Hevia et al. performed a randomized, double-blind, placebo-controlled study that showed healing times were significantly reduced after a 35% trichloroacetic acid peel if skin was pretreated with tretinoin 0.1% for two weeks.⁵⁴ Although healing times were reduced, there was no appreciable difference in cosmetic outcomes.

Salicylic Acid

Salicylic acid peels are typically used in 5-30% concentrations for the treatment of fine rhytids and dyschromia. A split face study performed by Oresajo et al. evaluating the clinical efficacy and tolerability of salicylic acid versus glycolic acid revealed similar clinical outcomes. A 5-10% salicylic acid peel was found to be just as safe and effective as a 20-50% glycolic acid peel.⁵⁵ It has also been suggested that a one-time application of 50% salicylic acid ointment, used after pretreatment with 20% trichloroacetic acid and tretinoin, is effective at treating lentigines and actinically damaged skin from the hands and forearms.⁵⁶

Pyruvic Acid

Pyruvic acid is an alpha-keto acid and is used as a medium chemical peeling agent. It has been used successfully in the treatment of rhytids, lentigines, and actinic keratoses. Prospective studies have shown that 50% pyruvic acid peels applied every 2 weeks, with four sessions on average,

produced significant improvement in the clinical appearance of photodamaged skin. Side effects were limited to erythema and stinging during the peeling procedure, with minimal discomfort reported in the post-peel period.^{57,58}

Phenol

Phenol is typically used to obtain a deep chemical peel. The use of this peel has decreased tremendously as laser and light devices have been developed that achieve similar results with fewer side effects. In skilled hands with careful patient selection, the phenol peel remains an effective means of treating disease processes that lie deeper in the dermis. It has also been suggested as an alternative treatment option for patients with numerous actinic keratoses. A prospective pilot trial performed by Kaminaka et al. evaluating 46 Japanese patients with actinic keratoses and Bowen's disease revealed that approximately 85% of patients were noted to clinically and histologically be clear of their actinic keratoses after 1 to 8 treatments with 100% phenol.⁵⁹

Side Effects

Superficial chemical peels can be used on all Fitzpatrick's skin types, and adverse outcomes are rare.⁶⁰ Patients must be carefully selected and warned about the development of erythema, irritation, and desquamation, which are normal and desired side effects of the peel. Medium and deep peels are associated with greater morbidity, healing time, and adverse outcomes such as scarring and dyspigmentation. Other postprocedure complications include an irritant contact dermatitis, secondary bacterial infection, and reactivation of the herpes simplex virus. In patients with a history of recurrent herpes labialis, prophylaxis with the appropriate antivirals should precede the chemical peel.⁶¹ Although toxic blood levels have never been shown after a phenol chemical peel, systemic absorption of phenol may be associated with cardiac toxicity, liver and kidney damage, and respiratory distress.⁶²

What We Know: Chemical Peels

- Several acids used for superficial and medium depth chemical peels are effective in treating photodamage, including glycolic acid, Jessner's solution, trichloroacetic acid, salicylic acid and pyruvic acid
- Deep chemical peels have largely been replaced by the use of laser and light devices and should only be used by experienced physicians
- Proper patient selection and physician experience are essential to minimize complications of medium and deep chemical peels

INJECTABLES

While topical treatments and chemical peels are good options for those patients who have dyspigmentation and superficial rhytides, more correction that is significant is needed to treat deeper rhytides. Injectables including botulinum toxin and injectable fillers are commonly used, and provide an alternative that is less invasive than surgery. The minimal invasion and the lack of downtime make injectables an attractive option for many patients.

Given the vast amount of literature available on botulinum toxin and injectable fillers, the goal of this summary was to focus on review articles published within the past 5 years discussing injectables. A review performed by Ogden et al. discusses the different types and uses of both botulinum toxin and injectable fillers.⁶³ Botulinum toxin is marketed as Botox[®] and more recently as Dysport[®] in the United States. One unit of Botox[®] is equivalent to 2.5-5.0 units of Dysport[®]. Botox[®] is primarily used to treat dynamic rhytids, which can be associated with both aging and photodamaged skin. The first large prospective, double-blinded, randomized, placebo-controlled trial was done in 2002 by Carruthers et al.⁶⁴ This study revealed that Botox[®] was effective at treating glabellar rhytids and that results were still visible 3 months after therapy. Adverse side effects were few and included headaches and blepharoptosis. Treatment doses vary depending on the area being treated and the individual patient. Crows feet have been treated successfully with a total dose of 6, 12, or 18 units per side.⁶⁵ Other studies have shown no clinical difference between 12 and 18 units.⁶⁶ Treatment of the glabellar area has been successful with 20-40 units of Botox[®] in females, and 40-80 units in males.^{67,68}

The first randomized-controlled trial examining Dysport[®] was performed in 2004 by Ascher et al.⁶⁹ These patients achieved softening of dynamic rhytids when treating the glabellar area. Fifty units of Dysport[®] was thought to be the adequate dose when treating glabellar rhytids, and headache was the most common side effect reported. Furthermore, a head-to-head comparison of Botox[®] and Dysport[®] was performed for the treatment of glabellar rhytids. Lowe et al. compared 20 units of Botox[®] with 50 units of Dysport[®] and found that at 12 weeks postinjection, the Botox[®] treatment group achieved a higher level of satisfaction with glabellar rhytid improvement. These results were also evident at 16 weeks postinjection.⁷⁰

There are a multitude of fillers available for the treatment of fine and coarse rhytids associated with photodamage and aging. Nonpermanent and biodegradable fillers include autologous fat, hyaluronic acid (Hyalform[®], Juvederm[®], Perlane[®], and Restylane[®]), and collagen products which have been taken off the market due to the superior performance of hyaluronic acid. Semipermanent and biodegradable fillers include calcium hydroxylapatite (Radiesse[®]), and poly-L-lactic acid (Sculptra/New Fill[®]). Semipermanent but nonbiodegradable fillers include polymethylmethacrylate micro spheres (PMMA) and collagen fillers (Artecoll/

Artefill® and Dermalive/Dermadeep®). The only permanent filler available is silicone, which is nonbiodegradable.¹ Fine rhytids are treated by injection of the filler intradermally; whereas deeper rhytids require injection in the deep dermis or subcutaneous space. All of the different fillers are effective at treating rhytids; the choice of which filler to use is shaped by patient needs and physician preferences.

Bovine collagen was available as Zyplast® or Zyderm® before being taken off the market in 2010. Zyderm® was used to treat superficial lines, whereas Zyplast® was used to treat deeper and coarser facial lines. Because the collagen is obtained from nonhuman sources, skin testing is required prior to therapy.⁶³ Adverse reactions included hypersensitivity, bruising, reactivation of latent herpes virus infection, and necrosis. Most cases of localized necrosis were reported in treatment of the glabellar area, therefore Zyplast® is not recommended for glabellar rhytids.⁷¹

Porcine collagen was another treatment option and was marketed as Evolence® before being discontinued. Porcine collagen has been associated with less hypersensitivity reactions than its bovine counterpart, however, not many studies have been done discussing its effectiveness.⁶³ Porcine collagen has been compared with Zyplast® and a small phase I clinical trial performed by Monstrey et al. revealed that porcine collagen may be more effective in improving wrinkle severity.⁷² Another study performed by Narins et al. comparing Evolence® and Restylane® showed no clinically significant difference in wrinkle severity.⁷³

Human collagen is no longer available but was marketed as Cosmoderm® and Cosmoplast®. Cosmoderm® was indicated for the treatment of fine and more superficial wrinkles, whereas Cosmoplast® was used for deeper wrinkles.⁶³ As this collagen was obtained from human sources, the incidence of hypersensitivity reactions was low. Cymetra® was another type of human collagen that typically required several treatments to obtain clinically evident results. A randomized trial done by Sclafani et al. compared the effects of Cymetra® (human collagen) with Zyplast® (bovine collagen) and found that measurable differences in the treatment of upper lip rhytids were significantly more prevalent in the Cymetra® treatment group.⁷⁴

Hyaluronic acid (Hyalform®, Juvederm®, Perlane®, and Restylane®) is a nonspecies-specific substance and therefore has a lower incidence of hypersensitivity reactions.⁶³ Restylane® and Juvederm®, have been compared to Zyplast® for the treatment of nasolabial folds in randomized-controlled trials. The study evaluating Restylane® was performed by Narins et al. Immediately following treatment, patients reported similar improvements in the wrinkle severity scale; however, at 6-month follow-up a higher proportion of patients reported improvement in the Restylane® treatment group.⁷⁵ Similarly, Pinsky et al. compared Juvederm Ultra® and Juvederm Ultra Plus® to Zyplast® in the treatment of nasolabial folds. Even after >9 months, 75% of the Juvederm Ultra® and 81% of the Juvederm Ultraplus® treatment areas maintained significant

correction, while the Zyplast® treatment areas did not. Side effects were comparable for the Juvederm® and Zyplast® products.⁷⁶ Hyaluronic acid fillers have also been shown to stimulate new collagen production in photodamaged skin.⁷⁷ Side effects from hyaluronic acid fillers are generally short lived and include edema, bruising, induration, and erythema.⁶³ There are reports of developing visible blue nodules with Restylane® if the filler is placed too superficially.⁷⁸ In these situations, hyaluronidase can be used to break up excessive or misplaced filler.

Polymethylmethacrylate microspheres (PMMA) are injected subdermally to treat coarse and deep rhytids. The microspheres may be suspended with bovine collagen (Artefill/Artecoll®) or hyaluronic acid (Dermalive®). Cohen et al. performed a randomized, multicenter clinical trial comparing the effectiveness of Artecoll® with bovine collagen. At 1-month follow-up, bovine collagen was found to be more effective at treating glabellar rhytids. However, at 3 and 6-month follow-up, Artecoll® was more effective at reducing the wrinkle severity in the nasolabial folds and the corners of the mouth.⁷⁹ Comparative studies for Dermalive® are lacking. PMMA fillers have been associated with nodular inflammatory reactions and granuloma formation.⁶³

Calcium hydroxylapatite (Radiesse®) is filler which is semipermanent and has been shown to have clinical results that last up to 1 year.⁶³ Comparative studies have been done looking at the effects of Radiesse® and Cosmoplast® (human collagen). Smith et al. performed a randomized, double-blind trial that showed significantly greater improvement of rhytids in the Radiesse® treatment group at both 3- and 6-month follow-up.⁸⁰ Side effects of Radiesse® include edema, erythema, and transient lumpiness. There have also been reports of submucosal nodule development, and therefore Radiesse® is oftentimes not recommended for lip augmentation.⁶³

What We Know: Injectables

- Botulinum toxin is useful in the treatment of dynamic rhytides
- Autologous fat, hyaluronic acid, calcium hydroxyapatite, poly-L-lactic acid, polymethyl methacrylate and collagen are all effective for improving the appearance of rhytides
- Selection of appropriate filler material is based on several factors, including location and depth of rhytides to be treated, desired duration of treatment effect and physician preference

LASERS, LIGHT SOURCES AND RADIOFREQUENCY DEVICES

The field of lasers, light sources, and radiofrequency devices has advanced rapidly in the last 20 years. Each

year there are new models introduced to the market, and many devices are appropriate for more than one indication. This section seeks to examine the best evidence for use of specific lasers, light devices, and radiofrequency devices for treatment of photodamage. In order to do so, the clinical manifestations of photodamage are separated here, with PubMed searches undertaken looking for randomized-clinical trials in the last 5 years, supporting the use of these modalities in addressing the individual manifestations of photodamage.

Treatment of Facial Telangiectasias

A wide variety of lasers and light sources are available to treat vascular lesions including facial telangiectasias from photodamage, erythema from rosacea, hemangiomas and port wine stains. Focusing on the relatively small caliber vessels that become evident, as part of photodamage, there are several devices that are used most commonly. Lasers in the 532-595 wavelength are popular choices because they effectively treat smaller, more superficial vessels with minimal bruising or down time. However, these wavelengths do not penetrate the skin deeply enough to treat larger, deeper vessels that the 940-1064 nm lasers can address. The long pulse dye 595 nm laser is a mainstay of treatment, while the pulsed KTP 532 nm, pulsed Nd:YAG 1064 nm, diode 800 nm, and pulsed alexandrite 755 nm are also frequently used.⁸¹

In order to compare laser and light treatments for facial telangiectasia, a PubMed search was conducted using the strategy (facial telangiectasia) AND (laser or light), and the search was limited to humans, randomized-controlled trials, English language publications in the last 5 years. This search revealed ten studies, four of which were omitted either because they did not compare efficacy of two treatments or because they limited their study to rosacea patients, when photodamage is the primary concern of this investigation.

Efficacy of IPL

Hedelund et al. evaluated 32 women in a split face RCT to demonstrate the efficacy of intense pulsed light (IPL) in the treatment of photodamage. Improvement in telangiectasia was one of several outcomes measured. Subjects received three IPL treatments to half of the face at 1 month intervals. The other half of the face received no treatment. Significant improvement in telangiectasia was demonstrated.⁸²

Comparison of LPDL and IPL

Nyman et al. evaluated 40 patients with facial telangiectasia in a randomized clinical trial with a split-face comparison of long-pulsed dye laser 595 nm and IPL, with single-blind evaluations. Patients received three treatments spaced 6 weeks apart, and evaluations were made 3 months after

completion of treatment. While both methods were effective in treating the telangiectasias and neither were associated with any adverse events in this study, excellent results (defined as 75% to 100% clearance of lesions) was noted in 46% of the LPDL group and 28% of the IPL group ($p=.01$). In addition, significantly fewer patients experienced pain with the LPDL, and 64% of patients preferred the LPDL while 21% preferred the IPL ($p<.001$).⁸³

Jorgensen et al. also conducted a study comparing LPDL 595 nm and IPL. This study included twenty patients who received three split-face treatments every 3 weeks. Outcomes were evaluated by the patient and by blinded evaluators at 1, 3, and 6 months. The LPDL achieved greater clearance of telangiectasias than IPL at 1, 3, and 6 months ($p\le .03$). In addition, pain scores were significantly higher for the IPL than for the LPDL ($p<.001$). No differences were noted in the efficacy of treating irregular pigmentation or skin texture, and neither was effective in reducing rhytides.⁸⁴

Comparison of Sequential Treatment with PDL 595 nm and Nd:YAG 1,064 nm to Each Treatment Alone

Karsai et al. compared sequential treatment of telangiectasias on the nose with PDL 595 nm and Nd:YAG 1,064 nm to treatment with PDL 595 nm alone and Nd:YAG 1,064 nm alone in a split-face design. Study participants received one treatment and were evaluated 4 weeks later by a blinded evaluator. The treatment group that received sequential treatment had greater improvement in lesions than did either group receiving single treatment ($p<.05$), and there was no difference in improvement between the single wavelength PDL 595 nm group and the Nd:YAG 1,064 nm group.⁸⁵

Comparison of Pulsed KTP 532 nm and PDL 595 nm

Uelehoer et al. compared the pulsed KTP 532 nm to the PDL 595 nm in a split face trial of 15 patients. Each was treated three times, and evaluated 3 weeks after treatment. The KTP laser was more effective, achieving 62% clearing after the first treatment and 85% 3 weeks after the third treatment, compared to 49% and 75% for the PDL. In terms of adverse events, the PDL had a more favorable profile. Seventy-nine percent of the KTP treatment group had swelling more than 1 day after treatment versus 71% of the PDL group, and 58% noted more erythema on the KTP side compared to 8% on the PDL side.⁸⁶

Comparison of IPL and AFT

Braun conducted a study with eight subjects who received split-face treatments with IPL and with fluorescent-pulsed

light, advanced fluorescent technology (AFT). Each subject received 3 to 5 treatments, three weeks apart. No differences were seen in efficacy of treating telangiectasia, dyspigmentation, or skin texture, and there were no adverse events noted in either treatment group.¹¹²

Comparison of 532 nm and 940 nm Diode

Tierney et al. conducted an RCT comparing 532 nm and 940 nm diode lasers for treatment of facial telangiectasias. Twenty-four treatment sites received two treatments and were evaluated for efficacy and for side effects 2 months after treatment. The 940 nm laser treatment sites achieved a mean clearance of 63%, while the 532 nm treatment sites achieved a mean clearance of 47.8% ($p < .05$). The two lasers were equally effective in treating smaller caliber vessels, but the 940 nm laser was superior in treating the larger vessels. In addition, pain and post-treatment erythema were significantly less in the 940 nm group, and significant crusting and swelling was only noted in the 532 nm group.¹¹³

In summary, IPL has been demonstrated to be effective in treating facial telangiectasia, with AFT showing equal efficacy. PDL 595 is more effective than IPL, and causes less pain. PDL 595 nm and Nd:YAG 1064 nm show similar efficacy, but sequential treatment with PDL 595 nm and Nd:YAG 1,064 nm is more effective than either treatment alone. Finally, KTP 532 nm is more effective than PDL 595 nm but has greater side effects.

Pigmentation

Dyspigmentation is a common feature of photodamage. Ephelides, lentigos, and mottled pigmentation are often

noted in chronically sun-exposed skin, and are usually displeasing to patients. Several lasers and light devices can be used to treat the dyspigmentation of photodamage. This section seeks to review recent studies these modalities.

A PubMed search was conducted using the following search strategy: (photodamage OR lentigo OR dyschromia) NOT (vitiligo OR melasma or acne) AND (laser OR light). The search was limited to randomized-controlled trials involving humans published in English in the last 5 years. This revealed 29 studies. This search was further limited by excluding studies that involved diseases other than photodamage, such as skin cancer, dermatosis papulosa nigra, and hemangiomas. It also excluded studies that did not have a laser or light sources as at least one of its treatment groups, studies that evaluated adjunctive therapies and techniques such as hydroquinone pretreatment and the use of cooling, and studies that did not measure dyschromia as one of the outcome measures. This limited the number of studies reviewed to ten.

Several lasers and devices have been studied recently for the treatment of facial pigmentation. This includes various long-pulsed Nd:YAG lasers, long-pulsed dye lasers, the Er:YAG laser, the KTP 532 laser, and intense pulsed light (IPL). Most of the studies comparing two treatment modalities reported good results with both, and no significant difference in efficacy between the treatments, as demonstrated in Table 41-2. It is important to note, however that many of these studies had other outcome parameters where significant differences were noted.

Dover et al. compared IPL with topical 5-aminolevulinic acid (5-ALA) to IPL alone in a split-face study of 20 subjects. Four treatments were administered 3 weeks apart. The first two treatments consisted of IPL preceded by 5-ALA or IPL alone. The second two treatments were IPL alone to the whole face. More improvement was noted

TABLE 41-2—Studies Comparing Treatments for Dyspigmentation with no Significant Difference in Efficacy

First Author	Year	Treatments Compared	N	Study Design	
Geraghty LN	2009	1,440 nm Nd:YAG fractional laser	1,320/1,440-nm multiplex Nd:YAG fractional laser	20	2 treatment arms
Jorgensen GF	2008	LPDL	IPL	10	Split Face
Galeckas KJ	2008	PDL with a compression handpiece	IPL	10	Split Face
Hantash BM	2008	Er:YAG	IPL	10	2 treatment arms
Braun M	2007	IPL	AFT		Split Face
Mezzana P	2008	IPL	IPL+low intensity diode+topical agents	100	2 treatment arms, patients matched for age, skin type and degree of damage
Butler EG 2 nd	2006	KTP 532 nm	IPL	17	Split Face

in the pretreatment side in the global photoaging score as well as treatment of fine lines and mottled pigmentation.⁸⁹ In a different study, Ruiz-Rodriquez et al. demonstrated no effect a red light device using either 1 hour or 3 hour pretreatment with 5-methyl aminolevulinate.⁹⁰ Li et al. demonstrated the efficacy of IPL on Asian skin.⁹¹

Skin Laxity

A PubMed search using the strategy (skin laxity) and (laser or radiofrequency), limited to controlled trials, humans and English language publications yielded 25 journal articles. Studies that did not measure laxity as an outcome were excluded. In addition, studies that were conducted on body skin or only on periocular facial skin were also excluded since the laxity evaluated was unlikely to involve a component of photodamage. The eight remaining studies were reviewed.

Four studies evaluated the effectiveness of different radiofrequency devices in treating facial skin laxity. Bogle et al. utilized a monopolar radiofrequency device with multiple passes on 66 subjects with moderate laxity of the lower face and neck. 92% had measurable improvement in overall appearance at 6 months, and 84% had improvement as measured by independent photographic review.⁹² Friedman and Gilead demonstrated the efficacy of a hybrid radiofrequency device for treating rhytides and lax skin on sixteen subjects, each of whom received between two and six treatments at 2 to 3 week intervals. Over half of patients noted significant or excellent improvement in laxity in the cheek and jowl areas.⁹³ Alexiades-Armenakas et al. compared unipolar versus bipolar radiofrequency devices for the treatment of laxity and rhytides. Ten subjects each received multiple passes per treatment at 1 week intervals for 4 weeks total. Both showed improvements in laxity and rhytides but the results were not statistically significant. This could be because of the small size of the study.⁹⁴ In a more recent study, Alexiades-Armenakas compared a fractional radiofrequency device to surgical face-lift for the treatment of skin laxity. The FRF device provided 16% improvement in skin laxity, which was statistically significant. Not surprisingly, the face-lift provided a greater improvement, with an average of 49% improvement in laxity.⁹⁵ These studies suggest that radiofrequency devices offer an effective alternative to traditional surgery for the treatment of skin laxity, although the results are more modest than the more invasive gold standard.

While the majority of recent studies evaluate radiofrequency devices for the treatment of skin laxity, Goldberg et al. Chan et al. and Alexiades-Armenakas have each conducted studies demonstrating efficacy of infrared devices in improving facial skin laxity.⁹⁶⁻⁹⁸ Alexiades-Armenakas has also demonstrated significant improvement in facial laxity using a 1310 nm near-infrared laser with sapphire contact cooling.⁹⁹

Rhytides

Rhytides are the most troubling part of photoaging for many patients. In order to evaluate recent advances in the use of lasers and light devices, a search was performed using the strategy (rhytides OR fine wrinkles) AND (laser or light or radiofrequency). Limits included randomized-controlled trials, humans, English language, and studies published in the last 5 years. This search revealed seventeen studies, eight of which were excluded because either they did not use rhytides as an outcome measure or because they did not use a laser, light or radiofrequency device as a treatment arm. Nine studies remained and are reviewed here.

Four studies demonstrated efficacy of specific treatments in reducing rhytides. Dual depth fractional carbon dioxide laser, 1310-nm wavelength laser with surface cooling, fractional resurfacing followed by PDT with 5-ALA and red light, and 5-ALA combined with IPL were all effective methods.^{89,99-101} In a study by Karsai et al. ablative fractional CO₂ and ablative fractional Er:YAG were equally effective in treating periorbital rhytides.¹⁰² In a study by Hantash et al. no difference was noted in the efficacy of Er:YAG versus IPL for treatment of rhytides.¹⁰³

Two studies did not yield statistically significant improvement in rhytides. In a study by Alexiades-Armenakas et al. radiofrequency did not demonstrate improvement in rhytides either with unipolar or bipolar handpieces, though a trend toward improvement was noted.⁹⁴ In a study by Jorgensen et al. neither LPDL nor IPL demonstrated reduction of rhytides, although they were effective in treating pigmentation and telangiectasia as noted previously.¹⁰⁴

One study in recent years has demonstrated superiority of one method over another in the treatment of rhytides. Hedelund et al. compared CO₂ laser treatment to IPL treatment in a study of 27 women randomized to one of the two treatment groups. The patients treated with the CO₂ laser had greater reduction of their rhytides, but also had more side effects.¹⁰⁵

CONCLUSIONS

Ultimately, the physician uses the best available scientific evidence combined with experience and professional judgment to make suggestions to patients regarding disease prevention and treatment options. Photodamage is no exception. While there is strong evidence for the effectiveness of many methods of photodamage prevention and treatment, every good study leaves the reader, and undoubtedly the authors, with additional research questions left to be addressed. However, the unanswered questions do not prevent one from drawing conclusions based on the evidence available.

As with any medical condition, prevention of photodamage should be the primary goal, with appropriate treatment modalities being implemented when needed.

What We Know: Lasers, Light Sources and Radiofrequency Devices

Facial Telangiectasias

- LPDL is more effective than IPL
- Sequential treatment with PDL 595 nm and Nd:YAG 1,064 nm is more effective than either treatment alone
- KTP 532 nm is more effective than PDL 595 nm, but also has a less favorable profile of side effects
- No differences in efficacy are seen between IPL and AFT
- Diode 940 nm is more effective and has less fewer side effects than diode 532 nm

Pigmentation

- Nd:YAG 1440 nm, PDL, IPL, Er:YAG and AFT are all effective for treating dyspigmentation

Laxity

- Radiofrequency devices and infrared devices have been demonstrated to improve skin laxity
- Surgical face-lift remains the gold standard for treatment of skin laxity

Rhytides

- Fractional carbon dioxide laser, 1310-nm wavelength laser with surface cooling, fractional resurfacing followed by PDT, 5-ALA with IPL and ablative fractional Er:YAG, are all effective
- Neither radiofrequency nor LPDL were demonstrated to reduce rhytides
- Conflicting data exists regarding the effectiveness of IPL

Evidence suggests that photodamage can, in fact, be prevented. Certainly, clothing provides an obvious first layer of protection from the sun. Improved education of patients regarding the types of fabrics to look for, helping them to understand the meaning of UPF, and even guiding them to specific brands at the discretion of the individual physician are all ways that physicians can help patients improve the usefulness of their clothing. However, while there are good studies documenting the UPF of various clothing, more studies are needed to specifically address the effectiveness of clothing in preventing photodamage. Because of the variable amount of protection provided by different types of clothing, and because even with the best clothing many areas of the body remain sun-exposed, sunscreens remain the most important tool in the arsenal to protect against photodamage, with strong evidence of their effectiveness, particularly in preventing skin cancers. The patient is often overwhelmed by the array of products available, and the physician can be helpful in providing guidance regarding the most appropriate ingredients and formulations to meet the individual's needs and to address their specific risks. The use of oral and topical antioxidants is often appealing to patients and is certainly appropriate as a compliment to traditional photoprotective measures.

For patients with mild to moderate photodamage, and for those who are not interested in more aggressive forms of treatment, there is strong evidence for the use of a topical regimen to reduce the signs of photoaging. Topical retinoids, alone or in combination, are the cornerstone of a topical regimen. Depending on the level of patient compliance and whether additional treatments are necessary or will be tolerated by the patient, growth factors, antioxidants or other treatments can be added. Superficial or medium depth chemical peels can be added for patients

with more photodamage, patients looking for faster results, and patients who do not comply well with daily skin care routines. There is strong evidence for the effectiveness of several different peeling agents and the selection of the agent is generally based on desired outcomes, patient parameters and physician preferences. In general, it is recommended that patients undergoing chemical peels be started on topical retinoids first to enhance the penetration of the peels.

Moderate to severe photodamage often requires correction that is more aggressive. The appearance of deep wrinkles results not only from photoaging, but also from facial expression and chronologic aging. Evidence confirms that these lines can effectively be treated with injectable botulinum toxin and fillers, although much of the published data does not focus on photodamage specifically since they address the more cosmetic aspect of photodamage. With proper patient and product selection and a well-trained administrator, these products can achieve natural-looking results.

The field of lasers, light sources and radiofrequency devices is one that is perhaps most difficult to address using strict evidence-based measures. There is certainly strong evidence for the effectiveness of several treatment devices. However, comparing devices to determine what is "best" is difficult. The research available often uses different methods of evaluation for different clinical parameters, making direct comparison of studies difficult. In addition, each device may address several treatment indications, but no one device does all things equally well. Ultimately, there are many factors that are considered as the individual physician outlines a treatment plan for a specific patient. The patients' skin type, treatment indications, tolerance for side effects and expectations, as well as the modalities available to the physician and his or her experience level are some of the considerations that must be made.

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Chemoprevention of Skin Cancer

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INTRODUCTION

Although sun safety and sunscreen have been promoted since the 1940s, studies have shown insufficient implementation and efficacy of these measures.¹⁻³ Dermatologists have subsequently been faced with an increasing incidence of skin cancer worldwide and a large cohort of high-risk patients with irreversible histories of significant sun damage.^{4,5} In the United States, skin cancer is more common than all other cancers combined. Over 100,000 new cases of melanoma and over 1 million new cases of nonmelanoma skin cancer (NMSC), such as squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), were expected to occur in 2008.^{6,7} Both types of skin cancer are commonly associated with significant morbidity and high healthcare costs. NMSC is the fifth most costly cancer within the Medicare population with an annual cost of \$650 million per year.⁸ Additionally, mortality becomes a realistic threat for melanoma and advanced NMSC. Patients with malignant melanoma have a median survival of 6-8 months and <5% will survive for 5 years or more.⁹ Over 8,000 melanoma-related deaths were expected to occur in 2008.¹⁰ Thus, it is imperative that new prevention strategies continue to be developed.

Chemoprevention is a pharmacologic intervention that prevents, arrests, or reverses carcinogenesis.¹¹ Primary chemoprevention prevents initial carcinogenesis, secondary chemoprevention prevents premalignant cancers from becoming malignant, and tertiary chemoprevention prevents cancer recurrence in patients with no further signs of disease. Chemoprevention is particularly important for high-risk patients.^{12,13} Examples of chemopreventative agents used for other types of cancers include tamoxifen for breast cancer, finasteride for prostate cancer, and nonsteroidal anti-inflammatory drugs (NSAIDs) for colon cancer. An example of a chemopreventative agent used in dermatology is diclofenac, a NSAID, to prevent actinic keratoses from progressing to invasive SCC.¹⁴⁻¹⁸

The potential of skin cancer chemoprevention has been increasing over the past three decades because of better understanding of the molecular pathways leading to skin cancer.¹⁹ For all types of cancer, carcinogenesis involves

genome destabilization with various alterations in genes responsible for cell-cycle regulation, checkpoint regulation, detoxification of carcinogens, DNA repair, proto-oncogenes, and tumor suppressor genes.²⁰⁻²¹ Within this framework, however, it is now well-known that SCC, BCC, and melanoma have multiple, distinct, and sometimes overlapping molecular pathways of carcinogenesis.

SCC carcinogenesis appears to depend primarily upon p53 gene mutations in keratinocytes, since 90% of sunlight induced SCCs have cytosine-thymine transition mutations in this gene.²²⁻²⁴ Mutations in the Ras proto-oncogene, the epidermal growth factor (EGF) gene, the nuclear factor KB (NFKB) gene, the extracellular signal-regulated kinase (ERK) gene, and the cyclin-dependant kinase inhibitor gene may also contribute to SCC carcinogenesis.^{25,26} Additionally, SCC tumorigenesis has been associated with cyto-oxygenase (COX) overexpression.^{27,28}

Basal cell carcinoma carcinogenesis also appears to be associated with p53 mutations in keratinocytes, because over 56% of sunlight-induced BCCs have mutations in this gene.^{29,30} However, this is clearly not the only mutation causing BCC because greater than 33% of sporadic BCCs have patched protein transmembrane receptor (PTC) tumor suppressor gene mutations.³¹ Furthermore, mutations in the PTC tumor suppressor gene are known to cause the rare and inherited nevoid basal cell carcinoma syndrome (NBCCS), which is characterized by a propensity for multiple BCCs. Additionally, studies have shown deregulation of the hedgehog pathway in a large proportion of sporadic BCCs.³²

Melanoma carcinogenesis appears to be associated with p16 tumor suppressor gene (also known as CDKN2A or INK4A) mutations in melanocytes, since up to 40% of hereditary melanomas have mutations in this gene. Mutations in the p16 tumor suppressor gene also occur in a significant proportion of sporadic melanomas.^{33,34} Other genes which may play an important role in melanoma carcinogenesis include p53, PTEN, and mdm2.^{28,29} Additionally, studies have shown inappropriate activation of the MAP kinase pathway with subsequent overproduction of endothelial growth factor (VEGF) and matrix metalloproteinases (MMPs) in melanoma carcinogenesis.³⁵

Many distinct SCC, BCC, and melanoma carcinogenesis pathways overlap by sharing common mutations, like the p53 mutation. For this reason, processes or molecules upstream or downstream of these common mutations can serve as targets for combined SCC, BCC, and melanoma chemoprevention. Such targets include polyamine or prostaglandin synthesis, retinoid receptors, and components of the Ras and MAP kinase-signaling pathway.³⁶

Examples of potentially chemopreventative agents that exploit these targets include retinoids, 3-hydroxy-3-methyl-glutaryl coenzyme A (HMG-CoA) reductase inhibitors, cyclooxygenase (COX) inhibitors, difluoromethylornithine (DFMO), vaccines, and botanicals such as tea polyphenols, apigenin, ginger, curcumin, grape seed proanthocyanidins, and resveratrol. Retinoids have long been known to regulate epithelial differentiation. However, recent studies have shown that retinoids alter a variety of pathways involved in the later stages of carcinogenesis. The HMG-CoA reductase inhibitors, also known as the statin class of lipid-lowering agents, are thought to disrupt angiogenesis and the isoprenylation of the Ras and Rho small GTPases. COX inhibitors are well known anti-inflammatory and analgesic agents that have recently gained support as chemopreventive agents against colorectal, bladder, and skin cancers. Recent studies have shown that childhood vaccines may reduce melanoma incidence and mortality by stimulating immune responses to cancerous and precancerous melanoma cells. Difluoromethylornithine, an ornithine decarboxylase inhibitor is an old compound that has gained recent support as a chemopreventive agent. Botanicals have also shown promise in the prevention of ultra violet (UV) radiation-induced skin damage and cancer. This review article will explore the above topics with emphasis on the most recent chemoprevention studies.

RETINOIDS

Retinoids are defined as natural or synthetic molecules with structural or functional similarities to Vitamin A (retinol). Natural retinoids include and retinoic acid (RA) and retinol itself, which the body derives from dietary retinyl palmitate, retinyl acetate, or carotenoids in animal products, supplements, or vegetables. Synthetic retinoids include tretinoin (Retin A or all-*trans* retinoic acid), isotretinoin (Accutane or 13-*cis* retinoic acid), alitretinoin (Panretin or 9-*cis*-retinoic acid), acitretin (Soriatane),

etretinate (Tegison), tazarotene (Tazorac), bexarotene (Targretin), and adapalene (Differin).

The correlation between Vitamin A deficiency and squamous metaplasia was first described in 1925.³⁷ That same year, vitamin A-deficient animal models were shown to have higher rates of gastric carcinoma.³⁸ Eight years later, vitamin A administration was shown to reverse epithelial metaplasia.³⁹ The resultant theory that retinoids could be used as chemopreventive agents gained support with further investigations regarding how retinoids affect cellular function. It is now known that retinoids modulate cellular differentiation, G1 cell cycle arrest, and apoptosis by binding nuclear receptors affecting growth factors, caspases, signal transduction molecules, and extracellular adhesion molecules (Figure 42-1).⁴⁰⁻⁴⁶ The exact mechanism by which retinoids decrease cancer incidence, however, remains unclear. Japanese studies have proposed retinoid-induced reductions in COX-2 and PGE2 as a potential mechanism, as COX-2 and PGE2 are constitutively expressed in skin cancer cells.⁴⁷ Austrian studies have proposed retinoid-induced increases in p53 and caspases as a potential mechanism as p53 and caspases promote apoptosis.⁴⁸ An American study has proposed retinoid-induced gap junction inhibition as a potential mechanism, as gap junctions are utilized in growth related cellular communication.⁴⁹ Still other studies have proposed retinoid-induced activator protein-1 (AP-1) inhibition as a potential mechanism, as AP-1 is a transcription factor for many growth-related proteins.^{50,51} More recently, microarray studies have proposed retinoid-induced inhibition the Raf/Mek/Erk branch of the MAP kinase pathway as a potential mechanism, as the MAP kinase pathway promotes mitosis.⁵² Thus, it is possible that retinoids may have multiple mechanisms of skin cancer chemoprevention.

Oral Natural Retinoids

Conflicting or insufficient data exists regarding the value of oral natural retinoids as chemopreventive agents. In animal models, oral retinyl palmitate was shown to decrease chemical and UV-induced tumor burden.^{53,54} In another animal model, oral retinyl acetate was shown to reverse epidermal hyperplasia, papilloma, and dysplasia, but not SCC in situ or SCC.⁵⁵ In human patients, however, limited data exists. Only one study has indicated that oral retinyl palmitate increased human RA serum concentrations.⁵⁶

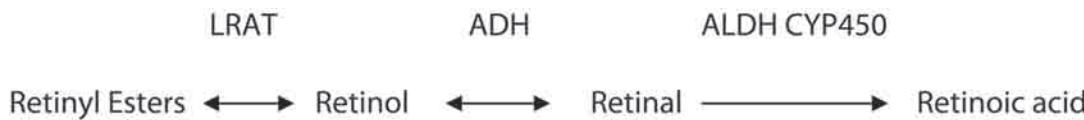


FIGURE 42-1 The retinoids; LRAT = lecithin retinol acyl transferase; ADH = alcohol dehydrogenase; ALDH = aldehyde dehydrogenase; (DeLuca)

More evidence is thus needed before recommendations can be made regarding oral retinyl palmitate or retinyl acetate as chemopreventive agents.

In animal and *in vitro* models, oral carotenoids have been shown to prevent UV-induced cutaneous erythema, immunosuppression, and carcinogenesis.^{57,58} Similarly, in human patients with erythropoietic protoporphyria, oral carotenoids have been shown to decrease photosensitivity.⁵⁹ Nevertheless, the chemopreventive value of oral carotenoids in patients with normal skin is controversial. Although several randomized clinical studies involving patients with normal skin have shown oral carotenoids to decrease UV-induced erythema, many well-powered studies involving such patients have not shown oral carotenoids to decrease the risk of skin cancer.^{60–68} Furthermore, several clinical studies have demonstrated a positive correlation between oral carotenoids (lutein, zeaxanthin, and beta-cryptoxanthin) and SCC.⁶⁹ These results were consistent with *in vitro* studies showing carotenoids to have prooxidant effects.^{70–72} Beta carotene-treated murine models had increased incidences of DMBA and TPA-induced papillomas, but decreased incidences of papilloma transformation into carcinoma.⁷³ Consequently, more evidence is needed before recommendations can be made regarding oral carotenoids as chemopreventive agents.

A randomized-controlled trial of 2297 moderate-risk patients reported that 25,000 IU of oral retinol was effective in preventing squamous cell carcinoma (SCC), but not basal cell carcinoma (BCC).⁷⁴ Individuals treated with oral retinol were 74% (HR 0.74, 95% CI = 0.56–0.99, P = 0.04) as likely to develop a new SCC compared to placebo with a 5-year follow-up period. Another randomized-controlled trial of 525 subjects did not demonstrate a significant difference between placebo and treatment with 25,000 IU oral retinol.⁷⁵ The follow-up period of this study was shorter, however, and could account for the difference in results. Furthermore, this study enrolled only 525 subjects compared with the 2297 subjects examined in the previous study. Based on these results, it is clear that further investigation is warranted in the evaluation of oral natural retinoids as chemopreventive agents.

Oral and Topical Synthetic Retinoids

Unlike natural retinoids, oral and topical synthetic retinoids have been proven as effective chemopreventive agents for high-risk patient groups by a significant number of studies. These high-risk patient groups include xeroderma pigmentosum (XP) patients, NBCCS patients, organ transplant recipients (OTRs), and recessive dystrophic epidermolysis bullosa (RDEB) patients.

Xeroderma pigmentosum patients are ideal chemoprevention candidates caused by a DNA repair enzyme defect, which places them at a 1000-fold increased risk of

skin cancer compared to the general population. A controlled, prospective study of five XP patients showed a 63% decrease in tumor incidence with 2 mg/kg oral isotretinoin treatment for 2 years.⁷⁶ However, in the 1 year following treatment cessation, the incidence of skin tumors rapidly increased 8.5-fold. This decreased effect without active treatment suggests that oral isotretinoin does not correct underlying DNA repair defects but, rather, acts later in the multistep carcinogenesis pathway.

Nevoid basal cell carcinoma syndrome patients are ideal chemoprevention candidates because of a tumor suppressor gene defect, which predisposes them to multiple BCCs.⁷⁷ Two case reports have demonstrated a marked response of NBCCS patients to oral etretinate at 1 mg/kg/day and oral isotretinoin at 0.4 mg/kg/day respectively.^{78,79} Oral isotretinoin at 0.2 mg/kg/day was reported to be much less effective than 0.4 mg/kg/day.⁸⁰ Two additional case reports showed that NBCCS patients treated with oral retinoids experienced a reduction in tumor burden and incidence during active treatment.^{81,82} Additionally, these patients developed less aggressive tumors that were more amenable to surgical treatment even after cessation of retinoid therapy. Peck et al. described a significant chemoprotective effect with lower doses of oral isotretinoin (0.25 to 1.5 mg/kg/day) in a study including non-NBCCS patients with multiple BCCs.⁸³ It is important to note, however, that this result may have been caused by the involvement of non-NBCCS patients. Thus, there is convincing evidence supporting the chemoprotective effect of oral synthetic retinoids in NBCCS patients.

Organ transplant recipients are ideal chemoprevention candidates because of immunosuppressive regimens resulting in significantly elevated incidences of significantly more aggressive skin cancers.^{84–87} A study of 455 Australian heart transplant recipients showed the overall incidence of skin cancer to be 31% at 5 years and 43% at 10 years.⁸⁸ Furthermore, skin cancer was the cause of 27% of deaths after 4 years of follow-up. Studies investigating oral retinoids in OTRs initially used etretinate and later used acitretin. In the 1990s, four noncontrolled studies of oral etretinate in OTRs showed a dramatic decrease in SCC incidence compared to before treatment.^{89–92} Five noncontrolled studies of oral acitretin in OTRs showed a dramatic decrease in SCC incidence compared to before treatment.^{93–97} Two, subsequent, randomized, controlled studies of oral acitretin in OTRs showed a statistically significant decrease in skin cancer incidence compared to the control group. The oral acitretin dosages used in these studies were 30 mg acitretin/day for 6 months and 25 mg/day for 2 years, respectively.^{98,99} A third randomized-controlled study of oral acitretin in OTRs showed a statistically significant decrease in actinic keratosis incidence, but not in skin cancer incidence.¹⁰⁰ Thus far, no studies have compared oral etretinate to oral acitretin. However, today it seems the chemopreventive

retinoids of choice are oral acitretin and oral isotretinoin. A recent survey of 28 dermatologists experienced in managing OTRs indicated that, of the 80% using chemopreventive retinoids for OTRs, 88% used primarily oral acitretin and 12% used both oral acitretin and oral isotretinoin.¹⁰¹ In 2004, De Graaf et al. published a comprehensive review of both oral and topical retinoid skin cancer chemoprevention for OTRs.¹⁰² Two randomized-controlled trials using 0.05% topical tretinoin daily and 0.3% topical adapalene daily both reported a significant reduction in actinic keratoses after 3 and 6 months, respectively.^{103,104} These findings support the recommendation that synthetic retinoids should be routinely used to prevent skin cancer in OTRs.

Recessive dystrophic epidermolysis bullosa patients are ideal chemoprevention candidates caused by chronic blistering and ulceration resulting in significantly elevated incidences of significantly more aggressive SCCs.¹⁰⁵ Approximately 85% of RDEB patients develop a SCC by the age of 45 and most die within 5 years of this first SCC.^{106,107} Only one, phase-1, clinical trial involving 20 RDEB patients on 0.5 mg/kg/day oral isotretinoin for 8 months has been performed to date.¹⁰⁸ This trial showed the studied dose of isotretinoin to be safe and well tolerated in RDEB patients. Although there were theoretic concerns that retinoids would exacerbate RDEB skin fragility, this side effect was shown to be transient, resolving without any decreases in isotretinoin dose. Additionally, some of the study participants reported reduced blister formation while receiving 0.1-0.2 mg/kg/day of oral isotretinoin. Further investigation is thus warranted regarding the chemopreventive efficacy of retinoids for RDEB patients.

Some of the aforementioned chemoprevention studies maintain patients on high dose oral retinoids for a significant amount of time. It is well documented that this practice can lead to numerous problems. In particular, hyperostosis, elevations in serum lipids, liver toxicity, teratogenicity, ocular effects, and depression are just a few of the serious side effects that may arise with long-term systemic retinoid therapy. In regard to topical retinoid use, the most common side effects are skin irritation and dryness. The recent Veterans Affairs Topical Tretinoin Chemoprevention Trial (VATTC) had to be discontinued because of elevated mortality in the tretinoin-treated group even after controlling for age, comorbidities, and smoking status. The authors, however, did not infer a causal link between topical tretinoin and death as a result of current evidence suggesting this to be unlikely.¹⁰⁹ There are several comprehensive reviews on the topic of adverse effects related to retinoids in the literature.¹¹⁰⁻¹⁶ Thus, this topic will not be fully explored in this article. It is imperative, however, that the risks and benefits of systemic retinoid therapy as chemoprevention of skin cancer are weighed carefully before beginning therapy. Although chemopreventive therapy with a potentially toxic agent may be justifiable in high-risk groups, it is difficult to justify use

in the general population or in patients at moderate risk for skin cancer.

HMG-CoA REDUCTASE INHIBITORS

HMG-CoA reductase inhibitors, otherwise known as statins, inhibit the rate-limiting enzyme of the cholesterol-producing mevalonate pathway (Figure 42-2).¹¹⁷ Because of their known efficacy in lowering cholesterol and their limited side effect profiles, statins are among the most commonly prescribed medications worldwide and are distributed without prescription in the UK.

Examples include lovastatin (Mevacor), simvastatin (Zocor), and atorvastatin (Lipitor).

A significant number of in vitro and animal studies have suggested mevalonate pathway inhibition to also result in skin cancer prevention (Table 42-1). For example, lovastatin and simvastatin have been shown to exhibit dose-dependent cytostatic and cytotoxic effects reversible with mevalonic acid addition.¹¹⁸ More specifically, these drugs are thought to prevent skin cancer by preventing the mevalonate pathway from producing farnesyl pyrophosphate and geranyl pyrophosphate (Figure 42-2).¹¹⁹ Farnesyl pyrophosphate activates Ras GTPases, which can promote cell cycle progression and subsequently neoplastic pathogenesis.¹²⁰⁻¹²³ Geranyl pyrophosphate activates Rho GTPases, which can promote cytoskeletal modifications and cell cycle progression via cyclin-dependant kinase inhibitor breakdown. These Rho GTPase functions can subsequently promote neoplastic pathogenesis and neoplastic invasion.¹²⁴⁻¹²⁶ In the 1990s it was suggested that decreased farnesyl pyrophosphate production was the main mechanism behind lovastatin's ability to induce G1 and G2 cell cycle arrest, reduce angiogenesis, and promote TNF-alpha antitumor activity.¹²⁷⁻¹²⁹ However, it has been more recently suggested that decreased geranyl pyrophosphate production plays a larger chemopreventive role. Studies demonstrating lovastatin's cytostatic effects showed these effects to be more compromised by geranyl pyrophosphate addition than farnesyl pyrophosphate addition.^{130,131} A 2004 study demonstrated simvastatin to convert drug-resistant multiple myeloma into drug-susceptible multiple myeloma via decreased Rho GTPase activation.¹³² Most recently, studies have shown decreased Rho GTPase-mediated CDK inhibitor breakdown and subsequently increased CDK inhibitor levels to be associated with G1 cell cycle arrest.^{133,134} Regarding metastasis prevention, studies have also shown Rho GTPase-deficient skin cancer cells to be unable to metastasize and Rho GTPase-negative animals to be less susceptible to skin cancer metastasis.^{135,136} Atorvastatin has been additionally been shown to decrease human melanoma metastasis in vitro and murine melanoma metastasis in vivo.¹³⁷

In vivo human studies, however, have produced varying results. A Cochrane review in 2005 showed no significant

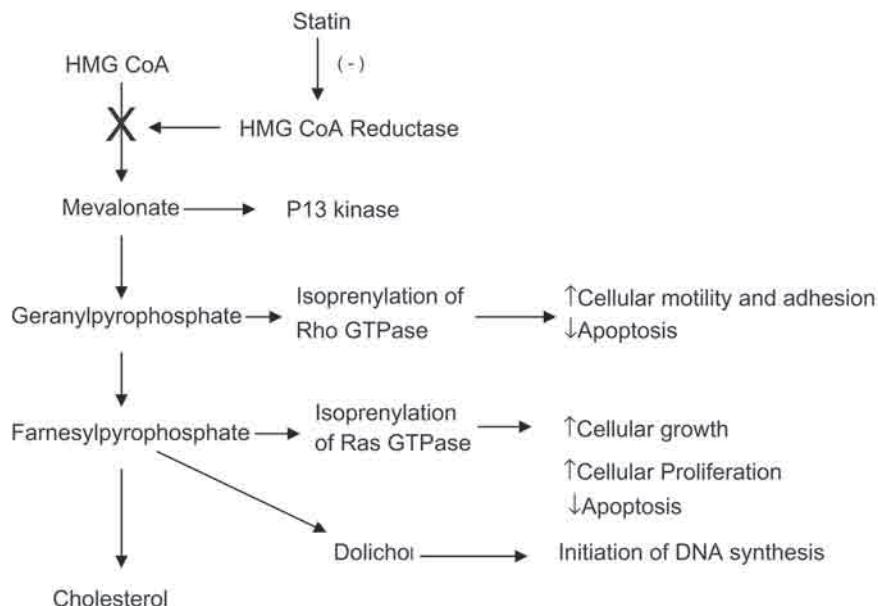


FIGURE 42-2 Pathway Inhibited by Statins

reductions in melanoma incidence and two meta-analyses in 2006 showed no significant reductions in general cancer incidence or mortality.^{138–140} Additionally, two large cohort studies in 2009 showed no significant reductions in BCC or keratinocyte carcinoma incidences.^{141,142} To date, the most convincing evidence regarding the chemoprotective properties of statins comes from cardiovascular studies. In a large, double-blind, randomized, placebo-controlled trial of lovastatin for the primary prevention of acute coronary events, patients exposed to lovastatin had significantly lower incidences of melanoma ($p < 0.05$).¹⁴³ Prompted by this observation, a retrospective, case-control study of 328 melanoma cases revealed that patients who developed melanoma had significantly lower exposures to statins (18% vs. 30%).¹⁴⁴ Thus, further research is warranted regarding the chemoprotective potential of statins for patients at high risk of developing skin cancer.

COX INHIBITORS

COX inhibitors, otherwise known as nonsteroidal anti-inflammatory drugs (NSAIDs), inhibit the principal enzyme needed to convert arachidonic acid into various prostaglandins. This enzyme exists in two forms, which have different patterns of activity. COX-1 is the constitutively expressed form, which produces prostaglandins for normal cell function and COX-2 is the inducible form, which produces prostaglandins for inflammation.¹⁴⁵ Nonselective COX inhibitors inhibit both forms. Selective COX inhibitors inhibit only COX-2. Examples of nonselective COX inhibitors include aspirin, ibuprofen, naproxen, indomethacin, diclofenac (Voltaren), and sulindac (Clinoril). Examples of selective COX-2 inhibitors include celecoxib (Celebrex), rofecoxib (Vioxx), and nimesulide (Mesulid). Rofecoxib and nimesulide, however, were

withdrawn from the market by 2004 because of concerns of cardiovascular and hepatic side effects.

Both nonselective and selective COX inhibitors are thought to have chemopreventive potential secondary to a number of proposed mechanisms. For example, COX inhibition has been proposed to prevent COX itself from producing reactive oxygen species (ROS), which could otherwise damage DNA and activate oncogenes.¹⁴⁶ It has also been proposed, however, that COX inhibitors selectively induce GSH deletion, ROS formation, and mitochondrial toxicity in melanoma cells.¹⁴⁷ Sulindac, specifically, has been shown to produce metabolites that down-regulate epidermal growth factor receptors.¹⁴⁸ COX-inhibitors have also been shown to decrease prostaglandins thought to inhibit antimelanoma macrophage and interferon- γ function.^{149,150} Additionally, in vitro studies have shown COX inhibition to decrease colon cancer angiogenesis, increase colon cancer apoptosis, and decrease melanoma invasion by unknown mechanisms.^{151–154} Other studies have identified potential chemopreventive targets for COX-inhibitors outside the COX pathway. These targets include extracellular kinases, AP-1, NFKB, and peroxisome proliferator activated receptor signaling pathways.^{155–158}

Despite the commonality of these potential mechanisms to COX-1 and COX-2 inhibition, many studies have focused on COX-2 inhibition because COX-2 is more associated with cancer. For example, COX-2 is known to be overexpressed by dysplastic and neoplastic lesions of the colon, stomach, esophagus, breast, cervix, bladder, and skin.¹⁵⁹ Profound increases in COX-2 expression have also been noted following UVB exposure of human skin cell lines, in vivo murine skin cells, and in vivo human skin cells.^{160–163} Increased COX-2 expression has additionally been noted in papillomas, actinic keratoses, SCCs,

Table 42-1—Summary of <i>in Vitro</i> and <i>in Vivo</i> Studies Demonstrating Molecular Mechanisms by which Statins Prevent Tumorigenesis	
Lovastatin	
Induce cellular arrest in G1 and G2	
↑TNF- α anti-tumor activity	
↓Cell motility	
↓Cellular proliferation	
↓Cellular growth	
↓Tumor cell metastasis	
↑p27KIP1 → Suppression on DNA synthesis	
↑ Cyclin dependent kinase inhibitors	
↓Cyclin D1, ↓Cyclin E, ↓Cyclin A	
Cervistatin	
↓Angiogenesis	
Simvastatin	
↓Cellular proliferation	
↓Cellular motility	
↓Tumor cell metastatic potential	
Atorvastatin	
↓Tumor cell metastatic potential	
Mevastatin*	
↑Cyclin dependent kinase inhibitor p21CIP1/WAF1	
↑ Cell cycle arrest	

*Colon cancer cells *in vitro*

and melanomas.^{164,165} According to Denkert et al. COX-2 expression is increased in 93% of human melanoma cells with moderate to strong expression in 68% of these cells.¹⁶⁶ In fact, elevated COX-2 is the first immunohistochemical marker to differentiate early melanoma from benign melanocytic nevi with sensitivity and specificity over 90%.¹⁶⁷ Increased COX-2 expression, however, has not been demonstrated in BCC.^{168,169}

Numerous *in vitro* and animal studies have shown oral and topical COX-2 inhibitors to effectively decrease tumor production.¹⁷⁰ For example, oral celecoxib has been shown to significantly decrease keratinocyte proliferation and increase keratinocyte apoptosis following UV irradiation.¹⁷¹ In murine models, oral celecoxib has also been shown to exhibit a dose-dependent reduction of UV-induced tumor incidence.^{172–174} A dose-dependent response to oral celecoxib was also noted when evaluating subsequent time to tumor appearance and multiplicity following UV exposure.¹⁷⁵ Nimesulide, another oral COX-2 inhibitor, has similarly demonstrated efficacy in decreasing UV-induced murine SCC number, volume, and malignant progression.¹⁷⁶ Topical celecoxib has been shown to reduce edema, dermal neutrophil activity, PGE2 levels, sunburn formation, and tumorigenesis in UV-irradiated mice.^{177,178}

In *vitro* and animal studies of oral, nonspecific COX-inhibitors have also shown promise. For example, oral, nonselective COX inhibitors have been demonstrated to decrease keratinocyte proliferation, increase keratinocyte apoptosis, and reduce tumorigenesis by 78% in murine models.^{179,180}

Human studies of oral and topical COX-inhibitors, however, have shown mixed results. A 2005 cohort study of 86 patients with significant histories of SCC showed SCC patients to be significantly less likely than control subjects to have used nonselective oral COX inhibitors two or more times per week for over 1 year. This study also showed that, among participants without SCC, those regularly using nonselective oral COX inhibitors had significantly lower AK counts than nonusers.¹⁸¹ A 2006 cohort study of 702 patients with significant histories of SCC or BCC, however, suggested a weak and inconsistent chemopreventive effect of nonselective oral COX inhibitors on NMSC. An adjusted odds ratio for the association of SCC or BCC risk and nonselective oral COX inhibitor use at baseline and year of diagnosis was 0.89 and 0.92, respectively, for BCC and 0.95 and 0.94, respectively, for SCC.¹⁸² Similarly, a 2008 cohort study of 349 patients with significant histories of melanoma showed no association between nonselective oral COX-inhibitor use and risk of melanoma or melanoma metastasis.¹⁸³ Most recently, however, a 2009 cohort study of 1402 high-risk patients showed a significant NMSC chemoprotective effect for participants who reported nonselective oral COX-inhibitor use for less than the study duration. Interestingly, this study also showed nonselective oral COX-inhibitor use of shorter duration to be more protective than use of longer duration.¹⁸⁴ To date, a number of studies have shown the topical diclofenac to be effective in preventing *in vivo* human actinic keratoses from progressing to SCC (secondary SCC chemoprevention). A 1997 study of 3% diclofenac in 2.5% hyaluronic acid gel applied twice daily for up to 180 days reported that 81% of patients had complete actinic keratosis resolution and another 15% showed marked improvement.¹⁸⁵ Two randomized, multicenter, placebo-controlled studies of patients with actinic keratoses showed similar results.¹⁸⁶ Currently, there are no studies of the primary chemopreventive potential of topical diclofenac, or comparisons of topical diclofenac to other effective actinic keratosis treatments such as topical retinoids, 5-fluorouracil, or imiquimod. Thus, given the mixed results of human studies regarding oral COX-inhibitors and the promising results of human studies regarding topical COX-inhibitors, more research is warranted.

It is important to note, however, that although topical diclofenac has almost no side effects, oral COX-inhibitors can cause significant side effects. The two most common side effects of nonselective oral COX-inhibitors are dose-dependent dyspepsia and renal toxicity. An estimated 10–20% of nonselective oral COX-inhibitor users experience dyspepsia, which can evolve into gastric ulceration

and perforation, resulting in 103,000 hospitalizations and 16,500 deaths per year in the United States.¹⁸⁷ Although oral COX-2 inhibitors were consequently created in hopes of eluding this side effect, all oral COX-2 inhibitors except celecoxib were pulled from the market when randomized-controlled studies showed them to increase mortality secondary to cardiovascular disease.^{188–191} Thus, when administering oral COX-inhibitor therapy, potential risks and benefits should be carefully weighed according to each patient's preexisting risks.

DFMO

DFMO, otherwise known as eflornithine (Ornidyl), was originally created in the 1970s as a chemotherapy agent. Although it proved unsuccessful in this area, it was subsequently used as an oral African sleeping sickness treatment and a topical cosmetic depilatory (Vaniqua).¹⁹²

DFMO is an irreversible inhibitor of ornithine decarboxylase (ODC).¹⁹³ ODC is the rate-limiting enzyme in the polyamine pathway, which produces polyamines implicated in cellular growth and differentiation.¹⁹⁴ ODC expression is minimal in healthy cells, but greatly increased with cellular injury, regeneration, and tumorigenesis.¹⁹⁵

A chemopreventive role for DFMO was postulated when animal studies showed it to decrease polyamine levels at low doses and with no demonstrable toxicity over long periods of use.¹⁹⁶ It was also noted that decreased radiation-induced ODC activity in some XP patients decreased herpes virus reactivation and skin cancer incidence.^{197,198} DFMO treatment in an XP murine model was subsequently shown to reduce tumor load.¹⁹⁹ Since then, murine studies have shown ODC to be necessary in skin carcinogenesis and DFMO to be a potent chemopreventive agent against UV-induced skin carcinogenesis.^{200–205} Interestingly, DFMO has also been shown to have a synergistic chemopreventive effect with COX-inhibitors.

Several phase I human studies have shown DFMO to be well tolerated with a minimal dose-dependent risk of reversible hearing loss.^{206–210} To date, only one case of irreversible hearing loss has been reported.²¹¹ Regarding colorectal adenomas, a prospective, randomized, placebo-controlled trial of patients treated with DFMO and sulindac for 3 years showed a 70% reduction in incidence and a 90% reduction in recurrence.²¹² Regarding actinic keratoses, a randomized, placebo-controlled study of high-risk patients treated with topical 10% DFMO for 6 months showed a 23.5% reduction in incidence.²¹³ Although the current level of evidence does not support DFMO use at this time, it is encouraging and indicates a need for further investigation of DFMO as a skin cancer chemopreventive agent.

VACCINATIONS

In 1796, Edward Jenner defined a 'vaccination' as an antigenic inoculation stimulating the immune system to

prevent or ameliorate disease. The hypothesis that vaccinations can stimulate an anticancer immune mechanism has existed since 1874, when acute infections were noted to coincide with spontaneous cancer remission.²¹⁴ Purified *Streptococcus pyogenes* and *Serratia marcescens* antigens were subsequently administered to cancer patients, inducing febrile illness and sometimes cancer remission.^{215,216} Although such practices have largely been eclipsed by radiotherapy and chemotherapy, skin cancer vaccinations are still being pursued. In particular, many efforts have been made to develop a melanoma vaccination because of melanoma's incidence, mortality upon metastasis, and typical resistance to radiation and chemotherapy. The potential of this immunologic approach has been highlighted by clinical trials demonstrating the efficacy of melanoma immunotherapies such as interleukin-2 and passive immunization with melanoma-reactive T-cells.^{217–219}

Initial attempts to identify a melanoma vaccination looked for associations between nonspecific febrile illness, BCG vaccination, vaccinia vaccination, or influenza vaccination and decreased melanoma incidence or progression. Although retrospective studies were promising, phase III trials did not show significant benefits. In 2002, a case-control study of 603 melanoma patients and 627 control patients demonstrated an inverse correlation between childhood BCG or vaccinia vaccination and melanoma incidence.²²⁰ The odds ratios and 95% confidence intervals for patients who had received BCG only, vaccinia only, or both were 0.43(0.2–0.93), 0.58(0.35–0.96), and 0.44(0.26–0.72), respectively. In 2003, a study of the same patients by Krone et al. found a history of severe febrile illness to have a similar effect, but a combination of severe febrile illness and vaccination did not produce a cumulative effect.²²¹ Similarly, a 2005 cohort study of 542 melanoma patients demonstrated an inverse correlation between childhood BCG or vaccinia vaccination and melanoma survival.²²² The hazard ratios and 95% confidence intervals for patients who had received BCG only, vaccinia only, or both were 0.75(0.30–1.86), 0.55(0.34–0.89), and 0.41(0.25–0.69), respectively. Regarding influenza vaccination, the 2003 study by Krone et al. showed no association between a history of one influenza vaccination in the previous 5 years and melanoma incidence. A case-control study in 2000, however, showed a history of three to five influenza vaccinations in the previous 5 years to be associated with a 50% lower risk of melanoma.²²³ A 1993, phase III, multicenter, randomized control trial of BCG vaccine involving 327 stage I melanoma patients, showed no significant increases in time to progression ($p = 0.55$) and duration of survival ($p=0.82$).²²⁴ A 2004, phase III, randomized, controlled trial of BCG vaccine involving 734 stage I–III melanoma patients by the Eastern Oncology Group showed no significant increases in disease-free survival ($p=0.84$) or overall survival ($p = 0.4$).²²⁵

Efforts were subsequently refocused on provoking melanoma-specific immune responses with vaccines consisting of whole melanoma cells, melanoma peptides,

dendritic cells loaded with melanoma peptides, melanoma gangliosides, melanoma oncolysate, melanoma RNA, melanoma DNA, or viral vectors of melanoma DNA. These would theoretically be used to treat melanoma or prevent melanoma recurrence. However, although animal studies, retrospective studies, and phase I and II clinical trials have been promising, phase III clinical trials have shown mixed results. In terms of safety, all phase I and II trials have shown predominantly grade I and II toxicities at low incidences. In terms of efficacy, phase I and II trials have shown encouraging results including: tumor regression in 28% of metastatic melanoma patients treated with a MAGE3 melanoma peptide vaccine ($n=39$)²²⁶; progression free survival in 58% of melanoma patients treated with a MART1, gp100, and tyrosinase melanoma peptide vaccine ($n=120$)²²⁷; improved clinical outcomes in metastatic melanoma patients with immune responses to a similar peptide vaccine ($n=25$)²²⁸; improved relapse-free survival with in high-risk, resected melanoma patients with immune responses to a MART-1 vaccine ($n=60$)²²⁹; improved prognosis in relapsed, high-risk, resected staged IIA-IV melanoma patients; treated with a MART-1, MAGE-1, gp100, and tyrosinase melanoma peptide vaccine ($n=24$)²³⁰; 12% objective clinical response in stage IIIb-IV melanoma patients successfully immunized with a similar peptide vaccine ($n=39$)²³¹; improved survival in metastatic melanoma patients mounting immune responses to at least two of four melanoma peptides loaded onto autologous dendritic cells ($n=18$)²³²; 57% immunogenicity in stage IV melanoma patients vaccinated with autologous dendritic cells transduced with adenovirus encoding MART-1 ($n=14$)²³³; 63% vaccine-related CD8+ T-cell response in melanoma patients vaccinated with dendritic cells electrophorated with mRNA encoding gp100 or tyrosinase ($n=11$)²³⁴; 50% T-cell response and 14% resultant clinical response in metastatic melanoma patients vaccinated with protamine stabilized mRNA coding for Melan-A, tyrosinase, gp100, Mage A1, Mage A3, and Survivin ($n=21$)²³⁵; 21% immunogenicity with correlation between MART-1 immunity and time-to-progression in stage IV melanoma patients vaccinated with DNA plasmids encoding MART-1 and tyrosinase ($n=19$)²³⁶; 39% CD8+ T-cell response in melanoma patients vaccinated with mouse and human DNA plasmids encoding tyrosinase ($n=18$).²³⁷

To date, there have been eight, phase-III, randomized melanoma vaccine trials showing mixed results. A 2002 trial of an allogenic, whole-cell melanoma vaccine in 689 stage-II melanoma patients showed no significant improvement in tumor recurrence or overall mortality. However, for those patients expressing HLA-A2 or HLA-C3, this vaccine was associated with a significant increase in relapse-free survival.^{238,239} A 2007 trial comparing Canavaxin allogenic, whole-cell melanoma vaccine plus BCG vaccine to BCG vaccine alone in 1,656 stage III and IV melanoma patients also showed no significant improvement in overall melanoma relapse or survival.²⁴⁰ In fact, this vaccine was

associated with decreased disease-free survival in patients with stage III melanoma. A 1994 trial comparing a GM2 ganglioside (melanoma glycolipid) vaccine plus BCG vaccine to BCG vaccine alone in 122 stage III melanoma patients, showed a significant increase in disease-free interval and overall survival in those patients who had pre-existing or vaccine-induced anti-GM2 ganglioside antibodies.²⁴¹ A 2001 trial comparing a conjugated GM2 ganglioside vaccine to high-dose interferon- α in 880 stage IIb to III melanoma patients was terminated at a median follow-up of 14 months because of inferior survival of the vaccinated group.²⁴² A 1998 trial of an allogenic vaccinia melanoma oncolysate in 217 stage III melanoma patients showed no significant increase in disease-free interval or overall survival.²⁴³ Similarly, a 2002 trial of another allogenic vaccinia melanoma oncolysate in 700 stage IIB and stage III melanoma patients showed no significant increase in relapse-free survival and overall survival.²⁴⁴ A 2005 trial comparing an autologous, melanoma peptide-loaded, dendritic cell vaccine to standard dacarbazine chemotherapy in 108 stage IV melanoma patients showed no significant improvement in overall survival.²⁴⁵ Thus, these eight, phase III, randomized trials do not demonstrate reproducible, significant, overall benefits to the tested melanoma vaccines. There does seem to be promise in the Southwest Oncology Group trial's whole-cell melanoma vaccine in HLA-A2 and HLA-C3 expressing patients, however, suggesting that future trials may benefit from targeting certain patient subsets. For all melanoma vaccines overall, however, there is sufficient evidence to warrant further exploration of vaccinations as potential chemopreventive or primary cancer prevention strategies. Barriers to vaccine efficacy have included melanoma's defense mechanisms against the immune system: Inhibitory cytokines, inhibitory surface proteins, decreased HLA antigen presentation, and reduced expression of molecules required for immune cell adhesion.²⁴⁶⁻²⁵² Other barriers have included the body's normal defenses against autoimmunity, including regulatory T-cells, and CTLA-4.^{253,254} Continuing efforts will subsequently have to be made to overcome these barriers.²⁵⁵⁻²⁵⁷

BOTANICALS

In recent years, considerable interest has been focused on identifying naturally occurring botanicals for the prevention of photocarcinogenesis. Wide varieties of botanicals have been reported to possess anticarcinogenic and antimutagenic activities because of their antioxidant and anti-inflammatory properties. Botanical supplements possessing antioxidant properties are among the most promising group of compounds that can be exploited as ideal chemopreventive agents for skin cancer.²⁵⁸ Such botanicals include tea polyphenols, apigenin, ginger, curcumin, grape seed proanthocyanidins, and resveratrol. These dietary botanicals have demonstrated a photoprotective

potential against UV radiation-induced inflammation, oxidative stress, and photocarcinogenesis in several recent in vitro and in vivo studies.^{259–261} In the remainder of this review, we will briefly discuss the chemopreventive potential of some dietary botanicals.

Tea

After water, tea is the most commonly consumed beverage worldwide. Of the major types of tea, black tea is most popular, followed by green tea.^{262,263} Both types of tea are derived from the same plant, *Camellia sinensis*, but are fermented for different lengths of time, resulting in different concentrations and oxidation states of catechin/epicatechin antioxidants, which are more commonly called “polyphenols.”²⁶⁴ Green tea is thought to have higher polyphenol content and the monomeric green tea polyphenol (-)-epigallocatechin-3-gallate (EGCG) is thought to be the most potent polyphenol antioxidant.²⁶⁵ Green tea has subsequently undergone more thorough clinical investigation of its chemopreventive efficacy.²⁶⁶ Additionally, although oligomeric black tea polyphenols such as the theaflavins have reached clinical trials²⁶⁷, the most abundant black tea polyphenols, the polymeric thearubigins, have yet to be fully described.^{268–270}

Many chemopreventive mechanisms have been proposed for green and black tea polyphenols. One of the first chemopreventive mechanisms proposed for green tea polyphenols was inhibition of IL-1 alpha expression. This hypothesis was based on a murine study showing topical green tea polyphenols to significantly decrease anthratin/mezerin/benzoyl-peroxide-mediated increases in cutaneous IL-1 alpha.²⁷¹ Another proposed mechanism from the same group was inhibition of CD11b+ cell infiltration, inhibition of IL-10 expression, and induction of IL-12 expression. This hypothesis was based on a murine study showing topical EGCG to significantly decrease UVB-induced cutaneous CD11b+ monocyte/macrophage/neutrophil infiltration and IL-10 elevations, both of which are associated with UVB-induced immunosuppression and increased skin cancer risk. This study also showed topical EGCG to significantly increase UVB-induced IL-12 production, which is associated with Th1 immune responses and the repair of UV-induced DNA damage.²⁷² One follow-up study showed topical EGCG to decrease UV-induced DNA damage in mice with functional IL-12, but not in mice without functional IL-12, supporting the hypothesis that EGCG-mediated increases in IL-12 decrease UV-induced DNA damage.²⁷³ Another follow-up study supported the same point by showing topical EGCG to significantly inhibit photocarcinogenesis in terms of tumor incidence, multiplicity, and growth in mice with functional IL-12, but not mice without functional IL-12.²⁷⁴ These results were also supported by a second follow-up study in 2009.²⁷⁵ Another proposed mechanism was stimulation of cytotoxic tumoricidal T-cells. This hypothesis was based on a murine study

showing oral green tea polyphenols to significantly increase CD8+ T cells in tumors.²⁷⁶ A follow-up study testing both oral green tea polyphenols and topical EGCG showed similar results, with topical EGCG proving more effective than oral green tea polyphenols.²⁷⁷ A possible connection to the previous proposed mechanism is that IL-12 is known to increase CD8+ development.²⁷⁸ These studies supporting polyphenol-mediated CD8+ T cell development also supported the hypothesis that green tea polyphenols inhibit skin cancer metastasis and angiogenesis. They showed both oral green tea polyphenols and EGCG to downregulate matrix metalloproteinases, which facilitate basement membrane invasion, and vascular endothelial cell antigens, which facilitate angiogenesis for tumor growth. These results were supported by another murine study showing oral green tea polyphenols to inhibit angiogenesis.²⁷⁹ Previous studies had also shown in vitro treatment with green tea polyphenols to reduce tumor cell invasion by 50% and inhibit UVB-induced protein oxidation by decreasing matrix metalloproteinase production.^{280,281} Another proposed chemopreventive mechanism for green tea polyphenols was inhibition of urokinase, a hydrolase that similarly facilitates basement membrane invasion. This hypothesis was based on a study showing EGCG to directly inhibit urokinase.²⁸² Another proposed chemopreventive mechanism for green tea polyphenols was initiation of apoptosis and cell cycle arrest in cancer cells, possibly via increased caspase-3 expression. This hypothesis was based on an in vitro study on human cancer cells showing green tea polyphenols to induce apoptosis and G0-G1 cell cycle arrest.²⁸³ These results were supported by studies showing EGCG to increase keratinocyte caspase-3 expression and apoptosis in UV-irradiated human subjects.^{284,285} Another proposed mechanism for polyphenol-mediated cancer cell apoptosis was via inhibition of the nuclear transcription factors “nuclear factor kappa-light-chain-enhancer of activated B cells” (NF-KB) and activator protein-1 (AP-1), which are associated with cancer, decreased apoptosis, and inflammation when upregulated.²⁸⁶ This hypothesis was based on a study showing EGCG to inhibit UV-induced NF-KB and AP-1 activity in human fibroblasts.²⁸⁷ A subsequent study elaborated on this hypothesis by showing EGCG to markedly inhibit IL-1 beta-mediated activation of NF-KB, resulting in decreased IL-8, which is a major neutrophil chemoattractant.²⁸⁸ Green tea polyphenols are also thought to prevent carcinogenesis initiation by preventing carcinogen-DNA adduct formation and carcinogenesis promotion by decreasing activation of ornithine decarboxylase, cell signaling kinases (JNK/ERK/p38), and transcription factors.^{289–291} Green tea polyphenols are also known to inhibit UVB-induced COX-2, PGE2, PGF2α, and PGD production, and these molecules are known to be overexpressed in skin cancer.^{292,293} Lastly, given the higher rate of melanoma in females, it has been suggested that green tea’s antiestrogenic properties may contribute to its antimelanoma effects.^{294,295}

Black tea polyphenols and rhealavins have also been shown to inhibit the UVB-induced activation of AP-1, mitogen-activated protein kinase (MAPK), and extracellular receptor-activated kinase (ERK).²⁹⁶ These compounds are also known to inhibit human keratinocyte c-fos expression.²⁹⁷ A 2008 murine study showed black tea polyphenols to decrease benzo(a)pyrene-DNA adduct formation and subsequently cell proliferation to inhibit skin carcinogenesis.²⁹⁸ Another 2008 in vitro study suggested that black tea rhealavins and thearubins exert chemopreventive effects through cell-cycle arrest and induction of the mitochondrial death cascade in skin cancer cells.²⁹⁹

Numerous murine, in vitro, retrospective, and clinical trials have demonstrated the nontoxic, chemopreventive efficacy of green tea polyphenols against UV-induced skin cancer. In 1991, oral and topical green tea polyphenols were shown to significantly increase time-to-tumor-development and significantly decrease tumor yield in a dose-dependent fashion following UV exposure ($p<0.01$).³⁰⁰ A follow-up study showed oral green tea polyphenols to significantly decrease erythema, photoaging, tumor number, and tumor size in a dose-dependent fashion following UV-exposure.³⁰¹ Other studies soon confirmed these effects.³⁰²⁻³¹⁰ A 2003 study more specifically showed oral green tea polyphenols to decrease numbers of UV-induced papillomas by 80%, keratoacanthomas by 53%, and SCC by 32%. This study also showed tumor incidence to be decreased by 60% and multiplicity to be decreased by 86%.³¹¹ Similarly, a 2005 study showed oral green tea polyphenols to decrease tumor incidence (35%), multiplicity (63%), and growth (55%).³¹² Although the 1991 study showed oral administration to be more effective than topical application, several subsequent studies have shown topical application to be more effective, especially when applied in a hydrophilic vehicle.³¹³⁻³¹⁵ Similarly, several studies have indicated EGCG to be the most effective green tea polyphenol in terms of skin cancer chemoprevention.^{316,317} In addition to demonstrating the ability of green tea polyphenols to prevent skin tumor initiation and growth, murine studies have demonstrated the ability of green tea polyphenols to induce partial regression of established skin papillomas.³¹⁸ Such findings have been supported by in vitro studies demonstrating green tea polyphenols to promote G0-G1 cell cycle arrest, promote apoptosis, and reduce metastasis by human tumor cells.³¹⁹⁻³²⁴ Retrospective human studies have also supported this data. A recent retrospective case control study of 770 BCC patients, 696 SCC patients, and 715 control patients demonstrated an inverse association between the regular consumption of tea (at least 1 cup per day for over 1 month) and NMSC after adjustment for sunburns, age, and gender.³²⁵ Clinical trials have similarly demonstrated that green tea and its extracts confer resistance to erythema induction, increase apoptosis in irradiated cells, and reduce DNA damage secondary to UV radiation.³²⁶⁻³²⁹ A 2009 clinical trial showed topical

green and white tea to significantly decrease UV-induced oxidative DNA damage compared to vehicle-only treated skin (n=10).³³⁰

A number of murine trials have also demonstrated the nontoxic, chemopreventive efficacy of black tea polyphenols against UV-induced skin cancer. A 1997 murine study showed that black tea, even when consumed with milk—as it is consumed by many humans, had significant chemopreventive efficacy.³³¹ These efficacies were confirmed by several other murine studies.³³²⁻³³⁴ A 1994 murine study of oral black tea, green tea, decaffeinated black tea, and decaffeinated green tea showed all to decrease UV-induced tumor number and size and each to decrease UV-induced carcinoma numbers by 93, 88, 77, and 72% respectively.³³⁵ Although this study showed black tea to be more effective than green tea, most comparative studies have shown green tea to be more effective. One such study also confirmed what the 1994 study suggested, that caffeine might contribute to the chemopreventive properties of tea. Decaffeinated versions of green and black tea had substantially less chemopreventive efficacy than caffeinated versions, and oral caffeine by itself had a substantial inhibitory effect on UVB-induced carcinogenesis.³³⁶ Another murine study showed oral black tea to decrease UVB-induced keratoacanthoma incidence by 58%, UVB-induced SCC incidence by 54%, and papilloma growth by 35-70%. Tumor volume was decreased by 60% for nonmalignant tumors and 84% for carcinomas. Histologic examination revealed significantly decreased mitotic index (16-42%) and significantly increased apoptosis index (44-100%) in malignant and nonmalignant tumors.³³⁷ A recent study of the ill-defined polymeric black tea polyphenols showed these compounds to significantly increase UVB-induced skin carcinogenesis latency, and decrease UVB-induced skin carcinogenesis multiplicity and incidence.³³⁸

As a potential chemopreventive agent, green tea is an ideal candidate given its worldwide use and favorable side effect profile.³³⁹ Although the mechanism of antineoplastic action of green tea has not been fully elucidated, the current data supporting the efficacy of green tea as an anticarcinogenic and chemopreventive agent is convincing. Thus, further investigation of the potential role of green and black tea as chemopreventive agents against skin cancer is warranted.

Apigenin

Apigenin is a widely distributed plant flavonoid (5,7,4'-trihydroxyflavone) naturally present in numerous fruits³⁴⁰ (apples, cherries, grapes), vegetables³⁴¹ (broccoli, tomatoes), herbs (clove, parsley) and beverages³⁴² (tea, wine). It is a free radical scavenger that has been shown to possess natural antioxidant, antimutagenic, and anticarcinogenic properties.³⁴³⁻³⁴⁸ Several nonskin cancer clinical trials have proven apigenin to be safe in humans.^{349,350}

In a 1990 murine study, topical apigenin was shown to inhibit epidermal ornithine decarboxylase in a dose-dependent fashion, increase TPA/DMBA-induced skin tumor latency by 3 weeks, and decrease TPA/DMBA-induced skin tumor incidence and multiplicity.³⁵¹ In 1997, these results were reconfirmed regarding UV-induced skin carcinogenesis. Treatment of murine skin with apigenin prior to UVB radiation resulted in a 52% reduction of cancer incidence and an increase in tumor-free survival in comparison to control mice ($p < 0.01$).³⁵²

Additionally, apigenin has been shown to inhibit cyclin-dependent kinases leading to cell cycle arrest, accompanied by inhibition of p34/cdk2 kinase protein levels in UV-induced tumorigenesis in mice.³⁵³ Apigenin treatment of mouse keratinocytes resulted in accumulation of p53 tumor suppressor protein and expression of a downstream cdk inhibitor protein p21/WAF1.^{354,355}

A recent in vitro study also showed apigenin to enhance apoptotic tumor cell death and render TC-1 tumor cells more susceptible to cytotoxic T-cells.³⁵⁶ This study furthermore demonstrated apigenin to enhance antitumor DNA vaccine efficacy. Another in vitro study showed apigenin to strongly inhibit the PDGF-dependent increase in vascular endothelial growth factor (VEGF) which is crucial for angiogenesis.³⁵⁷ These mechanisms support the potential chemopreventive effect of apigenin in photocarcinogenesis.

Ginger

Ginger (*Zingiber officinale Roscoe*, *Zingiberaceae*) has long been used in Eastern Medicine for a variety of ailments. Multiple animal and in vitro studies have demonstrated topical ginger extracts to reduce cutaneous tumorigenesis following chemical induction.^{358–364} This activity has been associated with reduced levels of ornithine decarboxylase, NF-KB, COX-2, superoxide, lipoxygenase, and TNF- α , suggesting ginger's chemopreventive properties to be related to its anti-inflammatory properties.^{365–369} A 2004 study showed the ginger extract zerumbone to prevent both tumor initiation and promotion by antioxidant and anti-inflammatory pathways, resulting in a 60% lower incidence and a 80% lower multiplicity.³⁷⁰ A 2005 study also showed topical [6]-gingerol to inhibit angiogenesis of human endothelial cells and cause G1 cell cycle arrest by down-regulating cyclin D1.³⁷¹ Two other in vitro studies have also shown topical ginger extracts to inhibit AP-1.^{372,373} Numerous animal and in vitro studies have furthermore demonstrated topical ginger extracts to induce apoptosis by a variety of mechanisms.^{374–381}

The components of ginger reported to possess cancer chemopreventive properties include vanillyl ketones, [6]-gingerol, and [6]-paradol. These compounds all share a vanilloid structure similar to other natural chemopreventive agents.^{382,383} As a group, Vanilloids have been shown to induce apoptosis.³⁸⁴ Ginger, like green tea, is widely

consumed and has limited side effect profile. Thus, it is also an ideal candidate for continued experimentation as a potential chemopreventive agent for skin cancer.

Curcumin

Another potent vanilloid compound reported to have cancer chemopreventive properties is curcumin (*Curcuma longa Linn*). Curcumin is what makes the widely consumed spice, turmeric, yellow. In 2005, an *in vitro* study of three melanoma cell lines showed curcumin to induce a dose-dependent increase in apoptosis.³⁸⁵ This effect was thought to be caused by down-regulation of NK- κ B and I κ B kinase, which play a central role in cell survival and growth. A 2007 study of murine melanoma cells corroborated these results by demonstrating curcumin to down-regulate constitutive NF-KB activity and induce apoptosis with caspase-3 activation.³⁸⁶ Murine studies have also shown topical curcumin to increase cutaneous glutathione, decrease cutaneous ODC activity, and inhibit DNA adduct formation.^{387–389} Other murine studies have shown curcumin to decrease cutaneous hyperplasia and formation of c-Fos and c-Jun proto-oncoproteins. In one such study, DMBA/TPA-induced tumorigenesis was decreased by 15–59%.³⁹⁰ Curcumin has also been reported to inhibit ERK activity, reduce activating protein-1 (AP-1) levels, and decrease nuclear factor κ B (NF- κ B) activation. These proteins act as transcription factors and are responsible for the upregulation of COX-2 expression.³⁹¹ ERK regulates NF- κ B, which is thought to regulate COX-2 via several mechanisms.³⁹² Curcumin has also been shown to affect the cell cycle by decreasing the number of cells actively synthesizing DNA.³⁹³

A phase I clinical trial has provided preliminary evidence that curcumin is effective in improving the histologic condition of high-risk or premalignant lesions. This study also confirmed that curcumin is nontoxic to humans when administered 8000 mg/day for 3 months.³⁹⁴ A 2004, an *in vitro* study of highly metastatic murine melanoma cells, showed curcumin to significantly inhibit MMP-2 activity, membrane type-1 matrix metalloproteinase (MT1-MMP) expression, and focal adhesion kinase expression for up to 28 days after curcumin withdrawal, potentially explaining curcumin's antimetastasis effects.³⁹⁵ Thus, the preponderance of evidence suggests that curcumin has great potential as an over-the-counter adjunct to skin cancer chemoprevention.

Grape Seed Proanthocyanidins

Grapes (*Vitis vinifera*) are one of the most widely consumed fruits in the world. Grapes are rich in polyphenols 60–70% of grape polyphenols are present in grape seeds.³⁹⁶ These polyphenols are flavan-3-ol derivatives. The term catechin is the combined name for monomers of flavin-3-ol derivatives and the term proanthocyanidin represents dimers and oligomers of flavin-3-ol derivatives.³⁹⁷ Grape seed proanthocyanidins (GSP) have been shown to be more

potent antioxidants and free radical scavengers than ascorbic acid and vitamin E.³⁹⁸ Further, numerous in vitro and in vivo studies have demonstrated the chemoprotective effects of grape seed proanthocyanidins in photocarcinogenesis.³⁹⁹ Mittal et al. provided the first evidence of UV-induced skin cancer prevention with oral GSP in hairless mice. In this study, dietary GSP inhibited photocarcinogenesis in terms of tumor incidence (20–95%), tumor multiplicity (46–95%), and tumor size (29–94%).⁴⁰⁰ Furthermore, dietary GSP was also shown to prevent malignant transformation of UVB-induced papillomas to carcinomas in mice in terms of carcinoma incidence (45%), multiplicity (61%), and size (75%) compared to non-GSP treated mice following UVB-induced skin carcinogenesis.⁴⁰¹ A 2009 study showed oral GSP treatment of mice exposed to TPA/DMBA resulted in significantly lower inflammation, tumor burden ($p < 0.05$), tumor number ($p < 0.01$), total tumor volume per tumor-bearing mouse ($p < 0.01$), and rate of malignant progression from papilloma to carcinoma.⁴⁰²

Grape seed proanthocyanidins is thought to produce these chemopreventive effects by reducing UV-induced oxidative stress, protein kinase activation, nuclear factor-kappa B signaling pathway activation, and immunosuppression.⁴⁰³ A 2005 study suggested GSP to induce p53-dependent apoptosis via activation of Bax, Bcl-2, and caspase 3 pathways in JB6 C141 cells (a well-developed cell culture model for studying tumorigenesis in keratinocytes).⁴⁰⁴ A 2007 study suggested GSP to induce apoptosis in human epidermoid carcinoma A431 cells through alterations in the Cdki-Cdk-cyclin cascade and caspase-3 activation resulting in a loss of mitochondrial membrane potential.⁴⁰⁵ Thus, further investigations into the chemopreventive efficacy and mechanism of GSPs are warranted.

Resveratrol

Resveratrol (trans-3, 5, 4-trihydroxystilbene) is a naturally occurring compound found in grapes, wine, and a variety

of nuts and berries. It is produced by plants in response to injury or fungal infection, however, it does not present any cytotoxic effects in animal models.⁴⁰⁶ Resveratrol has shown remarkable cancer chemopreventive effects in a variety of preclinical studies.^{407–414}

Studies have shown that resveratrol possesses potent antimutagen, antioxidant, antiinflammatory, antiproliferative, induction of phase II drug-metabolizing enzymes and inhibition of COX activity.^{415,416} Resveratrol acts at each of the three phases of carcinogenesis: tumor initiation, promotion and progression phases, and suppression of the final steps, including angiogenesis and metastasis.⁴¹⁷ It has also been shown to activate apoptosis, inhibit kinase pathways, and induce cell cycle arrest in tumor cells.⁴¹⁸ Additionally, it has demonstrated inhibition of reactive oxygen species, COX, NFKB, and AP-1 activity in mammary epithelial cells.⁴¹⁹ A 2005 murine study by Aziz et al. demonstrated that resveratrol imparts significant protection against UVB exposure-mediated skin carcinogenesis in hairless mice via inhibition of survivin.⁴²⁰ Survivin is a biomarker of tumor progression with an established overexpression in several cancers, which is thought to participate in the onset, and progression of SCC, BCC, and melanoma.⁴²¹ In vivo studies by Reagan-Shaw and colleagues showed that treatment with resveratrol inhibited UV-mediated increase in cyclin-dependent kinases (cdk 2, 4, and 6), cyclins (D1 and D2), and the mitogen-activated protein kinase pathway in hairless mice skin.⁴²² A 2009 murine study showed resveratrol treatment of mice exposed to DMBA to result in significantly fewer tumors ($p < 0.001$) when the mice had functioning toll-like receptors. This suggests that toll-like receptors, which function innate and adaptive immune responses, play an important role in resveratrol chemoprevention.⁴²³ Interestingly, another 2009 study showed resveratrol to sensitize A431 human epidermoid carcinoma cells to UVB-induced cell death.⁴²⁴ Several other studies have suggested resveratrol to affect its chemopreventive effects via mitochondrial signaling pathways.^{425,426} Thus, although

What We Know

- In America, skin cancer is more common than all other cancers combined.
- Chemoprevention is defined as a pharmacologic intervention that prevents, arrests, or reverses carcinogenesis.
- Retinoids are promising in the prevention of non-melanoma skin cancers.
- HMG-CoA reductase inhibitors, the cholesterol lowering agents known as statins, may be useful in chemoprevention of melanoma by their effects on the Ras and Rho GTPases. These GTPases are involved in cell cycle progression.
- Selective cyclo-oxygenase 2 (COX-2) inhibitors may prove to be useful in the chemoprevention of nonmelanoma skin cancer but the systemic side effects and risks may outweigh the benefits.
- Melanoma vaccines are promising and the immunomodulating effects of several varieties of these vaccines has proven effective in some clinical trials.
- Botanical ingredients including: tea, apigenin, ginger, curcumin, grape seed proanthocyanidins, and resveratrol affect UV induced carcinogenesis and their anti-oxidative properties hold promise for chemopreventive uses.

its mechanism of action is unclear, resveratrol holds great promise as a chemopreventive agent against UV-induced damage to the skin and further study is warranted.

CONCLUSION

Skin cancer is by far the most common cancer afflicting humans today. Although public health officials have tried to improve patient education regarding sun protection, both melanoma and nonmelanoma skin cancers continue to increase in incidence. As one of the most aggressive cancers, melanoma is associated with very high mortality rates. Although nonmelanoma skin cancers are associated with minimal mortality, patients predisposed to these cancers because of genetic conditions or immunosuppression, often have much higher mortality rates. Furthermore, all patient populations have significant morbidity and costs associated with nonmelanoma skin cancers.

It is subsequently necessary to revisit the issue of skin cancer prevention and possibly revise current recommendations. Many agents show significant chemopreventive effects against skin cancer. However, many of these agents also show significant incidences of serious side effects. Thus, when considering a chemopreventive regimen, the patient and physician must weigh the risks and benefits. Additionally, there are many potentially beneficial chemopreventive agents, which do not have sufficient evidence-based support to advocate their use at this time. Subsequently it is essential that further investigation be pursued.

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Treatment of Actinic Keratosis

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INTRODUCTION

An actinic keratosis (AK) is a dysplastic keratinocytic lesion located in the epidermis.¹ By definition, actinic keratoses (AKs) do not involve the *full thickness* of the epidermis, a characteristic which distinguishes an AK from Bowen's disease (squamous cell carcinoma (SCC) *in situ*).² Also known as solar keratoses, senile keratoses, and actinic cheilitis (when confined to the lips), AKs typically appear as scaly papules on an erythematous base and are normally rough to the touch.³ They are generally distributed over sun-exposed areas on older adults. AKs have the potential to develop into squamous cell carcinomas. Treatment is typically recommended because the natural history of an individual AK is unpredictable.⁴

EPIDEMIOLOGY

The estimated prevalence of AKs in the United States was 39.5 million in 2004,⁵ corresponding to a prevalence of approximately 13% based on census data.⁶ In the U.K., the prevalence of AKs was approximately 15.4% in men and 5.9% in women in a 2000 study.⁷ The risk of AK formation is higher in older patients, patients with childhood freckling, and blue-eyed individuals.⁸

ETIOLOGY

Actinic keratoses are generally felt to result from chronic sun exposure (i.e., chronic UV light exposure), since greater cumulative UVB exposure is associated with a greater risk of AK formation.⁸ Ultraviolet radiation has been shown to induce p53 mutations,⁹ which may serve as the initiating event in the development of an AK.¹⁰ The same p53 mutations found in SCCs are also found in AKs.⁹

DIAGNOSIS

The diagnosis of AKs is typically based on clinical features.¹¹ Biopsies are necessary when the clinical picture is unclear and would help differentiate an AK from an SCC or BCC. Major risk factors associated with progression of

AKs to SCC include induration/inflammation, a diameter >1 cm, rapid enlargement, bleeding, erythema, and ulceration.¹²

SEARCH METHODOLOGY

A PubMed search was performed using the search term "actinic keratosis AND treatment." Only articles available in English were included. Titles and abstracts were reviewed for relevance. References were also gathered from the cited studies reviewed. Case reports or smaller case series studies were not considered unless there was a paucity of information related to a given therapeutic intervention.

Papers were evaluated using the strength of recommendation taxonomy (SORT).¹³ The quality of most *studies* was graded using a 1-3 scale, with 1 representing "good-quality patient-oriented evidence," 2 representing "limited-quality patient-oriented evidence," and 3 representing other evidence based on consensus guidelines, opinion, and usual practice. *Overall recommendations* were graded using the SORT scale of A-C, where A represented a recommendation based on consistent patient-oriented, good-quality evidence, B represented a recommendation based on "inconsistent or limited-quality patient-oriented evidence," and C represented other recommendations, such as those based on consensus, opinion, and/or usual practice.¹³ Unless otherwise stated, recommendations pertain to nonpregnant, immunocompetent individuals.

Research Questions and their Answers

Efficacy, side effects, cost, and duration of therapy are all important factors to consider when deciding upon the optimal treatment for a patient. The thickness, location, and distribution of AK lesions are also important considerations. The purpose of this chapter is to provide the physician with the evidence behind the treatments, so an informed recommendation can be presented to the patient. Financial considerations will not be discussed in this chapter, but the reader is encouraged to gain an understanding of the cost of different therapies.

Is there any way to help prevent AKs?

A number of studies have shown that sunscreen may help prevent new actinic keratoses from forming. In 1993, Thompson et al. compared the effect of sunscreen versus the sunscreen's inactive ingredients (base-cream) on the number of actinic keratoses over a 7-month period and found an average increase of 1.0 ± 0.3 actinic keratoses per participant in the base-cream group compared with an average decrease of 0.6 ± 0.3 actinic keratoses per participant in the group that used sunscreen, concluding that regular sunscreen use prevents the development of actinic keratoses.¹⁴ A randomized-controlled trial by Darlington et al. studied the effects of daily sunscreen use with or without beta carotene supplementation and discretionary sunscreen use with or without beta carotene supplementation, and found that beta carotene supplementation of 30 mg/day had no significant effect on AK counts in the study periods; the daily application of sunscreen resulted in a significant decrease in the mean AK acquisition rate when compared to discretionary sunscreen use during the first 2-year study period, but not in a statistically significant decrease during the second 2-year study period.¹⁵

What will happen if AKs are not treated?

It is generally agreed that AKs have the potential to regress or progress to SCC, although the rates at which AKs regress or progress have been debated. Recent data also suggest that clinically diagnosed AKs may progress to basal cell carcinomas (BCCs).¹

Regression

Most literature favors the concept that an actinic keratosis may regress, but there is speculation on whether this has actually been proven.^{16,17} Several studies report spontaneous remissions of actinic keratoses.^{18–20} In a community-based study in Australia, Frost et al. reported on the regression of 346 (74%) prevalent (present on the first skin examination 12 months prior) actinic keratoses in 35 participants; this was contrasted with a 29% regression of 180 incident lesions (new lesions found during the study).¹⁸ Marks et al. observed 1040 people over 40 years old for 12 months: 616 subjects had actinic keratoses; of these subjects, 224 had at least one actinic keratosis undergo spontaneous remission (for a total of 485 out of the 1873 total lesions, or 25.9%).¹⁹ And finally, a 15% regression rate was reported by Harvey et al. in a South Wales study.²⁰ Thus, the evidence seems to favor the concept that an actinic keratosis may regress, although this does not necessarily indicate that AK lesions should not be treated.

Progression

Despite the rate of spontaneous remission in the aforementioned Marks et al. study, over all there was a 21.8% increase

in the number of actinic keratoses in the study population over the 12-month observation period, and a 0.24% incidence rate of squamous cell carcinoma occurring per actinic keratosis present at the baseline examination.¹⁹ In a subsequent study, Marks et al. mapped AKs to determine whether an SCC arose at the same location; 10/17 SCCs arose in an area that had previously been diagnosed clinically as an actinic keratosis. Since 21,905 actinic keratoses were present on the first visit, the risk of an actinic keratosis transforming into an SCC was estimated to be less than 1/1000.²¹ Prospectively derived data from the Department of Veterans Affairs Topical Tretinoin Chemoprevention Trial indicated the risk of progression of an AK to an SCC (invasive or *in situ* disease) was approximately 0.60% at 1 year, and 2.57% at 4 years, and the risk of progression of an AK to invasive SCC was 0.39% at 1 year and 1.97% at 4 years.¹ Additionally, Mittelbronn et al. reviewed 165 cutaneous SCC cases by light microscopy and found that 82.4% of cases showed AK involvement, and 26.7% of the SCC cases were felt to be arising from a pre-existing AK, providing additional evidence that SCCs develop from pre-existing AKs.²²

Why treat AKs?

Actinic keratoses are typically treated to prevent SCC, although cosmetic or symptomatic reasons may also play a role in the decision to treat AKs.¹ Different treatment modalities have been shown to decrease the incidence of non-melanoma skin cancer (NMSC) when compared with controls.²³ Since the natural history of a given lesion is unpredictable,⁴ treatment is generally recommended.

What has been used to treat AKs?

Table 43-1 summarizes select common and uncommon treatment options that have been used previously in the management of AKs and that will be discussed in this chapter. Investigational therapies, unavailable or discontinued therapies, and therapies only discussed in small case reports or small case series will not be discussed.

What is the evidence behind the use of pharmacologic therapies?

5-Fluorouracil

5-Fluorouracil (5-FU) is by far the most studied pharmacologic therapy for actinic keratoses and was approved for use in the United States in the early 1970s.²⁴ 5-FU interferes with DNA and RNA synthesis by blocking the methylation reaction of deoxyuridylic acid to thymidylic acid and has the most pronounced effect on rapidly dividing cells.²⁵ A number of 5-FU formulations are available in the United States, including 0.5%, 1%, 2%, and 5% creams and solutions (Table 43-2). While all current 5-FU formulations are

TABLE 43-1—Therapeutic Options for Actinic Keratoses

Frequency of use	Pharmacologic	Nonpharmacologic
More Common	<ul style="list-style-type: none"> 5-fluorouracil cream and solutions Imiquimod cream Diclofenac sodium gel 	<ul style="list-style-type: none"> Cryosurgery
Less Common	<ul style="list-style-type: none"> PDT Topical retinoids (tretinoin, adapalene) Chemical peels (trichloroacetic acid, glycolic acid, Jessner's solution) Salicylic acid ointment Oral retinoids (etretinate) 	<ul style="list-style-type: none"> Surgery (curettage and surgical excision) Laser resurfacing (Er:YAG, CO₂) Dermabrasion

PDT, photodynamic therapy.

approved for the treatment of multiple AKs,^{25,26} the 0.5% cream formulation is approved for treating multiple AKs of the face and anterior scalp.²⁷

Variations in dosing schedules, even for a given concentration, are common, although 5-FU is typically applied once to twice daily for 2-6 weeks. For the 2% and 5% formulations, a typical reaction follows when the cream or solution is applied to the AK lesions or subclinical disease; erythema is noted and may be followed by “vesication, desquamation, erosion, and reepithelialization.”²⁵ When 5% 5-FU solution is applied on the face, the erosions typically commence after 7-10 days, and 3-4 weeks of therapy may be sufficient to clear AKs.²⁸ It is recommended that the 2% and 5% cream and solution formulations be used until the erosions begin, at which point therapy should be stopped.²⁵ There has been debate regarding whether intense inflammation is necessary to achieve a clinical response,²⁹ but in general, inflammation has been associated with a greater therapeutic effect.³⁰ Moisturizers, topical antibiotics, and hydrocortisone are often used concomitantly during 5-FU treatment for symptomatic care or management of reactions.³¹

Since 5-FU has been around for several decades, there are numerous studies that support its efficacy. More recent studies generally compare different formulations or

compare 5-FU to other treatment modalities. Table 43-3 lists studies that compare 5-FU cream to a vehicle control and is limited to studies involving 0.5% 5-FU. Table 43-4 lists studies that compare different concentrations of 5-FU. Table 43-5 provides a summary of the major 5-FU treatment schedule variation studies, in which a nontraditional treatment schedule was assessed and/or compared to established treatment protocols. Table 43-6 summarizes 5-FU studies that compared 5-FU to another treatment modality. Table 43-7 reviews 5-FU studies in which 5-FU was combined with another treatment modality.

Comments

Surprisingly, no RCTs were found that compared 5% 5-FU to a control, as was noted by Askew et al. in their systematic review of 5-FU studies.⁴⁴ Despite this, several conclusions can be drawn, because complete clearance rates are reported in several of the studies, and 0.5% 5-FU has been compared to placebo, albeit for a shorter duration.

The only study that compared 0.5% 5-FU to 5% 5-FU found no difference in the percent change in the number of AK lesions after treatment and the proportion of patients with total clearance, noted fewer *patient-reported* side effects with the 0.5% cream even though the incidence of common reactions was the same in both groups, and reported that a significant number of patients preferred the 0.5% formulation.⁴⁵ The study follow-up period was only 4 weeks but demonstrates that the 0.5% formulation is at least as effective as the 5% formulation in the treatment schedule utilized.

5-FU has been included in multiple RCTs and at least two systematic reviews.^{44,45} A 1- to 4-week treatment regimen with 0.5% 5-FU cream applied once daily is supported by a strong body of evidence and has a SORT rating A. A 2- to 4-week course of 5% 5-FU also has a SORT rating A. The use of 5-FU has been shown to be associated with a lower incidence of NMSC based on the Hantash et al. study, which showed a similar effect for a chemical peel and a CO₂ laser.²³ Both the 0.5% and 5% formulations are the most extensively studied, but the effectiveness of other 5-FU concentrations as a therapy for AKs can likely be extrapolated from the data, and randomized-controlled trials evaluating the effectiveness of 1% and 2% formulations are needed. Only one study was found that discussed a 1% 5-FU ointment. In that study, published in 1965, 1%, 2.5%, and 5% ointment formulations were used to treat AKs, and the patients who received the 1% and 2.5% ointment formulations initially showed clearance, but recurrences were noted.⁴⁶

Imiquimod

Imiquimod received initial approval in the United States in 1997 for the treatment of genital warts, but eventually gained approval for the treatment of “nonhyperkeratotic,

TABLE 43-2—Available 5-FU Formulations[25-27]

Concentration	Formulation	Typical treatment schedule
0.5%	cream	Once daily up to 4 weeks ²⁷
1%	cream	Twice daily for 2-6 weeks ²⁶
2%	solution	Twice daily for 2-4 weeks ²⁵
5%	cream, solution	Twice daily for 2-4 weeks ²⁵

TABLE 43-3—Clinical Studies Evaluating 5-FU Versus Placebo

Source	Study details	Level of evidence	[5-FU], formulation vs control	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Menter et al., 2008 ³²	Pooled data from two phase III ^{33,34} and one phase IV study ^{35,36} (all DB, RCT) evaluating efficacy and tolerability of 0.5% 5-FU vs placebo in the treatment of adult patients with ≥5 visible and/or palpable AKs on the face or frontal scalp	1	vehicle control cream	Once daily, 1 week	199	Mean reduction in AK lesions from baseline: 24.4% Patients with complete clearance: 2 (1.0%)	4 weeks after treatment completion or discontinuation	1-week treatment with 0.5% results in a statistically significant reduction in AK lesions when compared with a vehicle control (61.2% vs 24.4%, respectively); 100% patient compliance in phase IV study treatment group
Jorizzo et al., 2002 ³³	DB, RCT evaluating safety and efficacy of 1-, 2-, and 4-week courses of 0.5% 5-FU vs placebo in the treatment of adults with ≥5 AKs on face or frontal scalp	1	vehicle control	1, 2, or 4 weeks	69	AK lesion reduction from baseline: 21.6% Patients with total clearance of AK lesions: 0%	4 weeks after treatment completion or discontinuation	0.5% 5-FU formulation resulted in significant lesion reduction when compared to vehicle control
Weiss et al., 2002 ³⁴	DB, RCT evaluating safety and efficacy of 1-, 2-, and 4-week treatments with 0.5% 5-FU vs placebo in the treatment of adults with ≥5 AKs on face or frontal scalp	1	vehicle control	1, 2, or 4 weeks	58	Mean reduction in AK count, from baseline: 34.4% Patients with total clearance of AK lesions: 3.4%	4 weeks after treatment completion or discontinuation	0.5% 5-FU formulation resulted in significant lesion reduction when compared to vehicle control

	0.5%, cream	Once daily, 2 weeks	41	Mean reduction in AK count, from baseline: 83.6% Patients with total clearance of AK lesions: 19.5%
	0.5%, cream	Once daily, 4 weeks	40	Mean reduction in AK count, from baseline: 88.7% Patients with total clearance of AK lesions: 47.5%

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported)

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported)
AK, actinic keratosis; FU, fluorouracil; [FU], concentration; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up.

TABLE 43-4—Clinical Studies Evaluating Different 5-FU Concentrations

Source	Study details	Level of evidence	[5-FU], formulation	Treatment regimen* (actual)	N†	Select outcome measures	F/U	Comments/Conclusions
Loven et al., 2002 ³¹	Single-blind, randomized, split-face study evaluating efficacy, tolerability, and patient satisfaction for the 0.5% and 5% 5-FU creams in the treatment of adult patients with ≥6 visible or palpable AK lesions on the face	1	0.5%, cream	Once daily, 4 weeks (mean 19 days, range 9–28 days)	21	Change in the number of AK lesions after treatment: 67% Mean lesion count reduction from baseline, at 8 weeks: 8.8 Proportion of patients with total clearance of AK lesions: 43%	4 weeks	0.5% 5-FU cream more effective than 5% 5-FU cream in reducing mean lesion count (statistically significant difference); no statistically significant difference between 0.5% and 5% formulations when comparing the percent change in the number of AK lesions after treatment and the proportion of patients with total clearance; reduction of mean lesion counts from baseline to week 8 for 5% group not statistically significant ($p=0.054$)

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported)

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported)
AK, actinic keratosis; FU, fluorouracil; [FU], concentration; F/U, follow-up.

TABLE 43-5—Clinical Studies Evaluating 5-FU Treatment Schedule Variation

Source	Study details	[5-FU], formulation vs control	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Epstein, 2006 ²⁸	Split-face study evaluating 5% 5-FU twice daily vs 4x daily in the treatment of adult patients with multiple facial AKs	2 5%, cream	2x daily on side of face (mean 17 days, range 13-21 days)	7	Severity of erosions when compared with 4x side; more eroded for: 1 patient mid-way, 1 patient at treatment end, and 0 patients post-treatment	Average of 30-90 days post-treatment	1-3 month post-treatment visits failed to show difference; longer post-treatment observation needed
Jury et al., 2005 ³⁰	Randomized parallel group study evaluating daily vs weekly courses of 5% 5-FU in the treatment of adults with nonhypertrophic facial and scalp AKs	2 5%, cream	4x daily on side of face (mean 17 days, range 13-21 days)		Severity of erosions when compared with 2x side; more eroded for: 4 patients mid-way, 3 patients at treatment end, and 0 patients post-treatment	52 weeks	Daily application more effective than weekly application for scalp and face AKs; inflammation is likely necessary to achieve effect
Epstein, 1998 ³⁷	Study evaluating efficacy and side effects of intermittent “pulse” dosing of 5% 5-FU vs traditional twice daily dosing in the treatment of patients with facial AKs; reviewers blinded to before and after photographs	2 5%, solution	Twice daily, 3 weeks Twice daily for 1 day/week for 12 weeks	13 7	Median lesion count: 17.5 at baseline, 0 at 52 weeks Median lesion count: 17.5 at baseline, 3 at 52 weeks	52 weeks	Daily application more effective than weekly application for scalp and face AKs; inflammation is likely necessary to achieve effect
Pearlman, 1991 ²⁹	Open-label study evaluating “pulse” dosing of 5% 5-FU in the treatment of patients with ≥20 facial AKs	2 5%, solution	Twice daily, unclear duration	13	Efficacy score derived from before and after photographs viewed by dermatologists: 2 with striking result, 3 with clearly visible difference, 2 with questionable improvement, 6 with no difference Efficacy score derived from before and after photographs viewed by dermatologists: 3 with striking result, 2 with clearly visible difference	Not specified	Reaction severity correlated with efficacy; pulse-dosing not as effective as traditional dosing
				5			

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless “actual” reported)

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless “actual” reported)
AK, actinic keratosis; FU, fluorouracil; [FU], concentration; F/U, follow-up.

(Continued)

TABLE 43-6—Clinical Studies Evaluating 5-FU Versus Other Treatments

Source	Study details	Level of evidence	Intervention	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Krawtchenko et al., 2007 ⁴	Randomized study evaluating 5% imiquimod versus 5% 5-FU ointment vs cryosurgery in the treatment of adult patients with ≥5 AKs in one anatomic area of up to 50 cm ² on head, neck, or décolleté	2	cryotherapy	Cryospray for 20–40 sec per lesion; additional treatment if insufficiently cleared at 2 weeks	25	Clinical complete clearance at test of cure, 6 weeks after last cryosurgery: 68% (17/25) Histologically confirmed total clearance at test of cure, 6 weeks after last cryosurgery: 32% (8/25) Sustained clearance, total treatment field, 12 mo after end of treatment: 4% (1/25)	12 months	5-FU resulted in the highest clinical complete clearance rates, but imiquimod cream had higher sustained clearance rates
				5% 5-FU cream, twice daily, 4 weeks	24	Clinical complete clearance at test of cure, 4 weeks after last 5-FU application: 96% (23/24) Histologically confirmed total clearance at test of cure, 4 weeks after last 5-FU application: 67% (16/24)		
				Sustained clearance, total treatment field, 12 mo after end of treatment: 33% (8/24)				
				Clinical complete clearance at test of cure, 8 weeks after last imiquimod application: 85% (22/26)				
				Histologically confirmed total clearance at test of cure, 8 weeks after last imiquimod application: 73% (19/26)				
				Sustained clearance, total treatment field, 12 mo after end of treatment: 73% (19/26)				
				One sachet (0.25 g) 5% imiquimod cream three times weekly (8 hr overnight) over 4 weeks.	26			
				5% imiquimod				
Tangheretti et al., 2007 ³⁸	Randomized, physician-blinded study evaluating 5% 5-FU vs 5% imiquimod in the treatment of adult patients with ≥4 AKs in one 25 cm ² treatment area on face, forehead, or scalp	2	5% 5-FU	5% 5-FU, twice daily, 2–4 weeks 5% imiquimod, twice weekly, 16 weeks	19	Total AK count reduction at week 24: 94% Complete clearance at week 24, incidence: 84% Total AK count reduction at week 24: 66% Complete clearance at week 24, incidence: 24%	24 weeks	Total AK count reduction and complete clearance were significantly greater in the 5-FU group compared to imiquimod
Smith et al., 2006 ³⁹	Bilateral, open-label, evaluator-blinded study evaluating 5% 5-FU and diclofenac sodium 3% gel in the treatment of patients with ≥3 AKs on face and scalp	1	5% 5-FU Diclofenac sodium 3% gel	5% 5-FU twice daily, 28 days 3% Diclofenac sodium gel twice daily for 90 days	29	Clearance rates 30 days after therapy completion: 124/126 (98%) Clearance rates 30 days after therapy completion: 111/125 (89%)	30 days	DFS slightly less efficacious than 5-FU; no statistical analysis

TABLE 43-6—Clinical Studies Evaluating 5-FU Versus Other Treatments (Continued)

Source	Study details	Level of evidence	Intervention	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions	
Hantash et al., 2006 ²³	RCT, prospective 5-year trial evaluating placebo vs 5-FU vs TCA vs CO ₂ laser in the treatment of patients with facial or scalp AKs	2	none	5-FU	none 5% 5-FU twice daily, 3 weeks	5 9	AK reduction at 3 months, mean ± SD, %: n/a NMSC incidence rate: 1.57 AK reduction at 3 months, mean ± SD, %: 83.2 ± 12.5 NMSC incidence rate: 0.21 AK reduction at 3 months, mean ± SD, %: 89.0 ± 6.6 NMSC incidence rate: 0.04 AK reduction at 3 months, mean ± SD, %: 92.0 ± 10.3 NMSC incidence rate: 0.15	3 months	All treatments resulted in a significant reduction in AK counts; cancer incidence in control group significantly higher than in treatment groups
Ostertag et al., 2006 ⁴⁰	Prospective RCT evaluating laser vs 5-FU in the treatment of patients with multiple AKs on the face or scalp	2	5-FU	5% 5-FU cream twice daily for 4 weeks	27	Mean decrease in the number of lesions at 12 mo: 12.4 Mean percentage of lesions cleared per patient at 6 mo, 12 mo post-treatment: 79.2, 76.6	1 year	When comparing 5-FU vs laser resurfacing, there was no statistically significant difference in the mean decrease in AK numbers per patient; there was significant difference in the mean percentage of lesions cleared per patient	
			Er:YAG laser resurfacing	Laser resurfacing once (extra passes for hypertrophic lesions), energy varied from 7 to 28 J/cm ² in Erbium mode, 10–12 pulses/sec with 50% CO ₂ between 2–4 W	28	Mean decrease in the number of lesions at 12 mo: 14.2 Mean percentage of lesions cleared per patient at 6 mo, 12 mo post-treatment: 94.4, 91.1			

Smith et al., 2003 ⁴¹	Randomized study evaluating 5-FU vs ALA-PDT with different light sources in the treatment of patients with ≥4 nonhyperkeratotic AKs on the face or scalp	2	5-FU	0.5% 5-FU once or twice daily, 4 weeks PDT with ALA plus blue light	12	100% complete clearance: 50% Cumulative clearance rate: 79%	4 weeks post-treatment	5-FU and PDT achieved similar clearance rates; PDT plus laser light less efficacious than PDT plus blue light and 5-FU; no statistical analysis
Kurwa et al., 1999 ⁴²	Randomized, bilateral (right and left hands) study evaluating 5-FU vs ALA-PDT in the treatment of patients with AKs on the hands	2	5-FU	5% 5-FU cream twice daily for 3 weeks on first hand ALA-PDT red light	17	Mean lesional area: 1390 mm ² (SD, 1130) (baseline) to 297 mm ² (SD, 209) (after treatment); 70% reduction Mean lesional area: 1322 mm ² (SD, 1280) (baseline) to 291 mm ² (SD, 274) (after treatment); 73% reduction	6 months	No patients had complete clearance in either group; there was no statistically significant difference between ALA-PDT and 5-FU in the reduction of lesional areas at 6 months; wide confidence intervals and small treatment group limit interpretation.
								*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported) †N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported) AK, actinic keratosis; FU, fluorouracil; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up; PDT, photodynamic therapy; ALA, aminolevulinic acid; SD, standard deviation; TCA, trichloroacetic acid.

TABLE 43–7—Clinical Studies Evaluating 5-FU in Combination with Other Treatment Modalities

Source	Study details	Level of evidence	Intervention	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Jorizzo et al., 2006 ³⁶ (interim analysis in Jorizzo et al., 2004 ³⁵)	Prospective DB, RCT evaluating three cycles of 5-FU + cryotherapy vs 3 cycles of placebo + cryotherapy in the treatment of patients with ≥5 AKs on the face	1	Vehicle	Up to three cycles of the following: vehicle applied once daily for 7 days with cryosurgery 4 weeks post-treatment Up to three cycles of the following: 0.5% 5-FU applied once daily for 7 days with cryosurgery 4 weeks post-treatment	72	Clearance of all AK lesions in all treatment areas: 26.7% % reduction from baseline after cycle 2: 57.8% % reduction from baseline after cycle 3: 64.7% Clearance of all AK lesions in all treatment areas: 36.8% % reduction from baseline after cycle 2: 86.3% % reduction from baseline after cycle 3: 77.8%	4 weeks post-treatment after each cycle	0.5% 5-FU prior to cryotherapy resulted in a significantly greater clearance of all AK lesions and a greater % reduction from baseline compared to cryotherapy alone
Jorizzo et al., 2004 ³⁵ (interim results of Jorizzo et al., 2006 ³⁶)	Prospective DB, RCT evaluating one cycle of 5-FU + cryotherapy vs one cycle of placebo + cryotherapy in the treatment of patients with ≥5 AKs on the face	1	Vehicle followed by cryosurgery	Vehicle cream once daily for 7 days, with residual AKs at 4-week assessment treated with cryosurgery (1 to 2 second single spray, mean thaw time ~10 seconds) 0.5% 5-FU followed by cryotherapy	72	Absolute reduction in AK lesions: 13.1 (SD, 7.6) baseline, 9.1 (SD, 6.1) at 4-week assessment Percentage reduction in AK lesions at 4-week assessment, from baseline: 28.8% Percentage reduction in AK lesions at 6-month assessment, from baseline: 45.6% Absolute reduction in AK lesions: 13.7 (SD, 9.3) baseline, 4.3 (SD, 3.8) at 4-week assessment Percentage reduction in AK lesions at 4-week assessment, from baseline: 62.4% Percentage reduction in AK lesions at 6-month assessment, from baseline: 67.0%	6 months	Compared to cryosurgery alone, patients who received 5-FU for 1 week + cryosurgery had significantly greater reduction in the number and percentage reduction of AK lesions.
Bercovitch, 1987 ⁴³	DB, RCT (with bilateral comparison) evaluating 5-FU + control vs 5-FU + tretinoin in the treatment of patients with multiple AKs on the hands and forearms	1	5-FU + control cream 5-FU + tretinoin	5% 5-FU twice daily + control cream to arm 1 for average of 15.8 days (actual) 5% 5-FU twice daily + 0.05% tretinoin cream nightly to arm 2 for average of 15.8 days (actual)	20	Number of AKs, 15.7 ± 6.1 pretreatment, 3.4 ± 2.6 post-treatment (3 mo) Number of AKs, 15.3 ± 6.9 pretreatment, 4.2 ± 2.5 post-treatment (3 mo)	3 months	Arms treated with 5% 5-FU cream twice daily + 0.05% tretinoin cream nightly were superior to arms treated with 5% 5-FU cream twice daily + a control cream; statistically significant difference in response rates

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported).

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported). AK, actinic keratosis; FU, fluorouracil; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up; PDT, photodynamic therapy; SD, standard deviation; TCA, trichloroacetic acid.

nonhypertrophic actinic keratoses (AK) on the face or scalp in immunocompetent adults⁴⁷ although a more recent formulation is indicated for “clinically typical, visible, or palpable actinic keratoses (AK) of the full face or balding scalp in immunocompetent adults.”⁴⁸ Imiquimod is considered a toll-like receptor 7 agonist that activates immune cells.⁴⁸ Although the exact mechanism of action in treating AKs remains unknown,^{47,48} the topical application of imiquimod in animal studies has been shown to result in the production of cytokines, such as TNF and IFN, which may play a role in its efficacy for AK treatment.⁴⁹

Imiquimod is available in 3.75% and 5% creams. The 5% cream is approved for twice weekly application for 16 weeks.⁴⁷ Erythema and scabbing and crusting are the more common reactions; flaking, scaling, dryness, and erosions/ulcerations may also occur;^{11,50} these reactions may or may not limit further treatment. Clearance of lesions is more common in patients who develop local reactions, such as erythema, at the application site.⁵¹ The 3.75% cream is applied once daily before bedtime for 2 weeks, followed by a 2-week no-treatment period, then another 2-week treatment period with once daily application.⁴⁸ Similar types of side effects are expected when using the 3.75% formulation when compared to the 5% formulation.

In addition to the studies comparing 5-FU and imiquimod mentioned previously in this chapter, several double-blind, randomized controlled trials have been published comparing the efficacy of topical 5% imiquimod cream to vehicle controls and have yielded fairly consistent clearance rates. Nevertheless, dosing and treatment duration times have varied. Shorter treatment intervals and twice weekly dosing regimens have also been evaluated (Table 43-8). Two placebo-controlled randomized controlled trials were found evaluating 3.75% imiquimod, as well (Table 43-9).

Three meta-analyses for imiquimod as a treatment for AK were also found.^{51–53} The first, by Falagas, reviewed the efficacy of imiquimod established by earlier trials and showed (with a narrower confidence interval) that imiquimod was significantly greater than placebo for the complete clearance of AKs.⁵¹ Hadley et al. reported a 50% complete clearance rate with imiquimod use, based on 5 trials and 1,293 patients.⁵² Gupta et al. reported higher complete clearance rates based on a small number of studies, which included a case study, and performed a meta-analysis of 5-FU in the same manuscript.⁵³

The use of imiquimod is indicated for immunocompetent persons,⁴⁷ but there are reports of successful use in transplant recipients on continuous systemic immunosuppressive therapy.⁵⁴ At this time, more studies are needed before its use is considered an acceptable first-line choice for immunosuppressed patients.

Comments

Surprisingly, the highest clearance rates reported in the studies reviewed were for treatment schedules <16 weeks in

duration.^{59,63} Nevertheless, more follow-up data are available on the more traditional 16-week regimens.⁶¹ The treatment of facial or scalp AKs in immunocompetent adults with 5% imiquimod cream once daily, 2-3 days per week, for up to 16 weeks has a strength of recommendation rating (SORT) A, based on several randomized controlled trials that demonstrate consistent clearance rates and data on recurrence. Once daily, 3 days/week 5% imiquimod therapy may produce fewer recurrences than 2 days/week therapy.⁶¹ Two 4-week courses with 5% imiquimod have also demonstrated consistent clearance rates comparable to 16-week courses,^{57,59} but two shorter courses of therapy (3-4 weeks each) carry a SORT rating of B because the two randomized controlled trials yielded somewhat inconsistent results (although one evaluated two 3-week courses and the other evaluated two 4-week courses). Good quality evidence is limited on dosing with 5% imiquimod for longer than 16 weeks, and the outcomes with less frequent dosing for longer durations (once weekly for 6 months⁵⁶) are not as robust as more traditional treatment schedules, but still produce improvement. Treatment of facial or scalp AKs with the newer 3.75% imiquimod formulation for two 2-week treatment periods separated by a 2-week no-treatment period also has a SORT rating of A. The role of imiquimod in reducing the overall incidence of NMSC and its associated morbidity and mortality remains to be studied.

Diclofenac gel

Approved in the U.S. in 2000, 3% diclofenac sodium gel (DFS) is indicated for the topical treatment of AKs.⁶⁷ Diclofenac is a nonsteroidal anti-inflammatory drug and, in the topical gel formulation, is in 2.5% hyaluronate sodium;⁶⁸ it is recommended that the gel be applied twice daily for 60–90 days.⁶⁷

In addition to the studies comparing 5-FU and DFS mentioned previously, three randomized, double-blind, placebo-controlled studies that evaluated topical 3.0% diclofenac in 2.5% hyaluronan gel for the treatment of AKs were reviewed, along with one open-label study (Table 43-10). Pirard et al. conducted a meta-analysis of the three RCT studies listed in Table 43-10. For the two RCT studies reporting on a target lesion number score (TLNS), the mean quantity of gel applied was 0.5 g twice daily for an average of 75 days; the meta-analysis showed the diclofenac to be significantly more effective than the hyaluronan gel vehicle in producing a complete resolution of all target lesions in the treatment area (TLNS0), with 39.6% (42/106) having a TLNS0 30 days post-treatment. All three RCTs reported on a cumulative lesion score, as well, which included new lesions. The meta-analysis showed that the diclofenac was significantly more effective than the hyaluronan gel vehicle in producing a complete resolution of all lesions in the treatment area, which included new lesions (cumulative lesion number score, CLNS0). The average duration of treatment was 78 days, with an average of 0.42 g gel applied,

TABLE 43-8—Clinical Studies Evaluating Imiquimod 5% Cream

Source	Study details	Level of evidence	Treatment vs control	Treatment regimen*	N†	Select outcome measures	F/U (type)	Comments/Conclusions
Gebauer et al., 2009 ⁵⁵	Phase II, DB, RCT evaluating 5% imiquimod vs placebo in the treatment of adults with ≥10 but ≤50 clinical AKs on forearms and hands	1	Placebo cream 5% imiquimod	Once daily 2, 3, 5 or 7x /week for 8 weeks, on dorsum of forearms/hands Once daily 2x/week for 8 weeks, on dorsum of forearms/hands Once daily 3x/week for 8 weeks, on dorsum of forearms/hands Once daily 5x/ week for 8 weeks, on dorsum of forearms/hands Once daily 7x/ week for 8 weeks, on dorsum of forearms/hands	29 31 29 30 30	Complete clearance, % of patients: 0% Complete clearance, % of patients: 3.2% Complete clearance, % of patients: 6.9% Complete clearance, % of patients: 3.3% Complete clearance, % of patients: 6.7%	8 weeks (c, p)	Partial clearance rates were higher when the dosing frequency was higher.
Zeichner et al., 2009 ⁵⁶	DB, RCT evaluating imiquimod vs vehicle in the treatment of patients with ≥6 AKs on the face, head, or scalp	1	Vehicle 5% imiquimod	Once weekly, 6 months, on one side of face/head/scalp Once weekly, 6 months, on other side of face/head/scalp	15	Complete clearance rate, % of patients: 0% Complete clearance rate, % of patients: 6.7% (1/15)	4 weeks	46.7% (7/15) treated with imiquimod had marked improvement or greater, compared to 6.7% (1/15) treated with placebo
Alomar et al., 2007 ⁵⁷	DB, RCT evaluating imiquimod vs vehicle in the treatment of patients with 5-9 AK lesions within a contiguous 25 cm ² treatment area on the head	1	Vehicle 5% imiquimod	Once daily, 3/week, 4 weeks; repeated if not completely clear after first 4-week cycle Once daily, 3/week, 4 weeks; repeated if not completely clear after first 4-week cycle	130 129	Complete clearance rate 8 weeks post-treatment, % of patients: 2.3% (3/130) Complete clearance rate 8 weeks post-treatment, % of patients: 55.0% (71/129)	8 weeks after last treatment (c, p)	Percentage of patients with complete clearance after first cycle = 37.2% (48/129); shorter treatment courses had similar clearance rates compared to previous, longer-duration trials
Jorizzo et al., 2007 ⁵⁸	DB, RCT evaluating imiquimod vs vehicle in one or two 4-week courses in the treatment of patients with AKs on the head	1	Vehicle 5% imiquimod	3x/week for 4 weeks of treatment 3x/week for 4 weeks, followed by 4-week no-application period, then another 4-week course 3x/week for 4 weeks of treatment	123	Complete clearance rate after course 1, % of patients: 4.1% Overall complete clearance rate, % of patients: 14.6% Complete clearance rate after course 1, % of patients: 2.68% Overall complete clearance rate, % of patients: 53.7%	4 weeks after last treatment	Imiquimod 3x/week for 1 or 2 4-week treatment courses resulted in complete clearance rates slightly higher than a cited ⁵⁰ traditional 16-week course ⁵⁸

Stockfleth et al., 2007 ⁵⁹	2	5% imiquimod	Once daily, 3 d/week, 4-8 weeks (8 weeks if AK lesions remained after first 4-week course)	829	Complete clearance rate, % of patients: 68.9% (571/829)	4 week (c)	Shorter treatment courses had similar clearance rates compared to previous, longer-duration trials
						8 week (c)	
Korman et al., 2005 ⁶⁰	1	Vehicle	Once daily, 3 d/week, 16 weeks	250	Complete clearance rate, % of patients: 7.2% (18/250)	Recurrence (%), interval: 24.7 (19/77), median F/U 16 months ⁶¹	
		5% imiquimod	Once daily, 3 d/week, 16 weeks	242	Complete clearance rate, % of patients: 48.3% (117/242)		
Szeimies et al., 2004 ¹¹	1	Vehicle	Once daily, 3 d/week, 16 weeks	139	Complete clearance rate, % of patients: 2.2% (3/139)	8 week (c, p)	Imiquimod once daily, 3 d/week for 16 weeks is effective for face and scalp AKs
		5% imiquimod	Once daily, 3 d/week, 16 weeks	147	Complete clearance rate, % of patients: 57.1% (84/147)		
Lebwohl et al., 2004 ⁵⁰	1	Vehicle	Once daily, 2 d/week, 16 weeks	221	Complete clearance rate, % of patients: 3.2% (7/221)	8 week (c)	Recurrence (%), interval: 42.6 (23/54), median F/U 16 months ⁶¹
		5% imiquimod	Once daily, 2 d/week, 16 weeks	215	Complete clearance rate, % of patients: 45.1% (97/215)		

(Continued)

TABLE 43-8—Clinical Studies Evaluating Imiquimod 5% Cream (Continued)

Source	Study details	Level of evidence	Treatment vs control	Treatment regimen*	N†	Select outcome measures	F/U (type)	Comments/Conclusions
Chen et al., 2003 ⁶²	DB, RCT evaluating 5% imiquimod vs vehicle in the treatment of patients with 5–15 AKs on scalp, forehead and temples, or both cheeks	1	Vehicle 5% imiquimod	Once daily, 3 d/week, 3–6 weeks (6 weeks if <75% clearance after first 3-week course) Once daily, 3 d/week, 3–6 weeks (6 weeks if <75% clearance after first 3-week course)	10 29	Complete clearance rate, % of patients: 10% (1/10) Complete clearance rate, % of patients: 28% (8/29)	14 weeks after study initiation (c)	Subjects with ≥75% clearance significantly greater in imiquimod group when compared with placebo
Stockfleth et al., 2002 ⁶³	DB, RCT evaluating 5% imiquimod vs vehicle in the treatment of patients with 3–10 AK lesions on the scalp, forehead, dorsal forearm, neck, or the back of the hand in a treatment area that did not exceed 20 cm ²	1	Vehicle 5% imiquimod	3 d/week, 12 weeks 3 d/week, 12 weeks	11 25	Complete clearance rate, % of patients: 0% (0/11) Complete clearance rate, % of patients: 84% (21/25)	2-week (c, p); up to 2-yr follow-up in minority of patients ⁶⁴	Recurrence (%), interval: 8%, 1 yr ⁶⁴

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported).

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported). AK, actinic keratosis; FU, fluorouracil; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up; c, clinical; p, pathologic.

TABLE 43-9—Clinical Studies Evaluating Imiquimod 3.75% Cream

Source	Study details	Level of evidence	Treatment vs control	Treatment regimen*	N†	Select outcome measures	F/U (type)	Comments/Conclusions
Swanson et al., 2010 ⁶⁵	Two multicenter, DB, RCT evaluating imiquimod 2.5%, 3.75% and placebo in the treatment of adults with 5-20 AK lesions on either the face or scalp	1	Placebo	2-week once daily treatment application, followed by 2-week no-treatment period, then another 2-week once daily treatment period	159	Complete clearance rate (% of subjects): 6.3% Partial clearance rate (% of subjects): 22.6% Median % reduction in AK lesions vs baseline: 25.0%	8 week (c)	Imiquimod 3.75% cream significantly greater partial clearance rates and reductions in AK lesion counts vs 2.5% formulation and placebo
			Imiquimod 2.5%	2-week once daily treatment application, followed by 2-week no-treatment period, then another 2-week once daily treatment period	160	Complete clearance rate (% of subjects): 30.6% Partial clearance rate (% of subjects): 48.1% Median % reduction in AK lesions vs baseline: 71.8%		
Hanke et al., 2010 ⁶⁶	Two multicenter, DB, RCT evaluating imiquimod 2.5%, 3.75% and placebo in the treatment of adults with 5-20 AK lesions on either the face or scalp	1	Placebo	2-week once daily treatment application, followed by 2-week no-treatment period, then another 2-week once daily treatment period	160	Complete clearance rate (% of subjects): 35.6% Partial clearance rate (% of subjects): 59.4% Median % reduction in AK lesions vs baseline: 81.8%		
			Imiquimod 3.75%	3-week once daily treatment application, followed by 3-week no-treatment period, then another 3-week once daily treatment period	164	Complete clearance rate (% of subjects): 5.5% Partial clearance rate (% of subjects): 12.8% Median % reduction in AK lesions vs baseline: 23.6%		
			Imiquimod 2.5%	3-week once daily treatment application, followed by 3-week no-treatment period, then another 3-week once daily treatment period	164	Complete clearance rate (% of subjects): 25.0% Partial clearance rate (% of subjects): 42.7% Median % reduction in AK lesions vs baseline: 66.7%		
			Imiquimod 3.75%	3-week once daily treatment application, followed by 3-week no-treatment period, then another 3-week once daily treatment period	162	Complete clearance rate (% of subjects): 34.0% Partial clearance rate (% of subjects): 53.7% Median % reduction in AK lesions vs baseline: 80.0%		

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported)

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported)
AK, actinic keratosis; FU, fluorouracil; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up; c, clinical; p, pathologic.

TABLE 43-10—Clinical Studies Evaluating 3.0% Diclofenac in 2.5% Hyaluronan Gel

Source	Study details	Level of evidence	Treatment modality	Treatment regimen	Treatment duration*	N†	Select outcome measures	F/U	Comments/Conclusions
Gebauer et al., 2003 ⁷³	DB, RCT evaluating 3.0% diclofenac in 2.5% hyaluronan gel vs vehicle control in the treatment of patients with solar keratoses on the head, neck, hands, or arms for 5 cm ² area.	1	Hyaluronan gel	0.25 g twice daily	12 weeks	77	Mean lesion count reduction at EOT: 4.7 ± 6.9 Mean lesion count reduction at 16-week post-treatment visit: 2.4 ± 4.3 (23.6%) Complete resolution at EOT: 13% Complete resolution at 16-week post-treatment: 10%	16 weeks from baseline	At 16-weeks post-treatment, diclofenac gel significantly more effective than hyaluronan vehicle in reducing mean lesion count and producing complete resolution.
Rivers et al., 2002 ⁷⁴	DB, RCT evaluating 3.0% diclofenac in 2.5% hyaluronan gel vs vehicle control for the treatment of patients with ≥ 5 AKs within up to three 5 cm ² treatment areas in at least one body area, including the forehead, central face, scalp, and dorsum of hands	1	Hyaluronan gel Hyaluronan gel	0.5 g twice daily topical application 0.5 g twice daily topical application	30 days 60 days	49	See comments. Percentage of patients with complete resolution of all target lesions 30 days after end of treatment: $10\%^{74}$ $\geq 75\%$ clearance of target lesions: $22\%^{69}$ See comments.	30 days after EOT	For all indices measured (target and cumulative lesion scores, lesion total thickness score, investigator and patient global improvement indices), the proportion of patients achieving each outcome measure was greatest in the 60-day treatment arm, followed by the 30-day treatment arm, then the 60-day placebo arm, then the 30-day placebo arm; statistically significant difference was noted between the 60-day placebo and treatment arm, but not between 30-day placebo and treatment arms.
			3.0% diclofenac in 2.5% hyaluronan gel 3.0% diclofenac in 2.5% hyaluronan gel	0.5 g twice daily topical application 0.5 g twice daily topical application	30 days 60 days	49	Percentage of patients with complete resolution of all target lesions 30 days after end of treatment: $33\%^{74}$ $\geq 75\%$ clearance of target lesions: $56\%^{69}$	48	Percentage of patients with complete resolution of all target lesions 30 days after end of treatment: $33\%^{74}$ $\geq 75\%$ clearance of target lesions:

Wolf et al., 2001 ⁷⁵	DB, RCT evaluating 3.0% diclofenac in 2.5% hyaluronan gel vs vehicle control for the treatment of patients with ≥ 5 AKs in up to three 5 cm ² treatment areas (forehead, central face, scalp, arms, hands)	1	Hyaluronan gel	0.5 g twice daily	90 days	59	Percentage of patients with complete resolution of all target lesions 30 days after end of treatment: 20% ⁷⁵ $\geq 75\%$ clearance of target lesions: 48% ⁶⁹	30 days after EOT	When compared with the hyaluronan vehicle, the diclofenac treatment group had a significantly greater percentage of patients with complete resolution of all target lesions and complete resolution of target and new lesions
	Rivers et al., 1997 ⁷⁶	2	Open-label study evaluating 3.0% diclofenac in 2.5% hyaluronan gel in the treatment of patients with ≥ 1 AK on the head, neck, or hands	3.0% diclofenac in 2.5% hyaluronan gel	Up to 180 days	29	Complete response at 30 days post-treatment: 81% (22/27)	30 days after drug stopped	Topical diclofenac is useful for the treatment of AKs; patients with only 1 AK eligible to participate in study

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported)

[†]N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported)
AK, actinic keratosis; DB, double-blind; RCT, randomized controlled trial; F/LJ, follow-up; TLNS, Target Lesion Number Score (number of lesions in a designated area at the initial assessment); CLNS, Cumulative Lesion Number Score (total number of lesions in a designated area, throughout the study); EOT, end-of-treatment.

and 39.1% (70/179) patients treated had a CLNS0 30 days post-treatment.⁶⁸ The authors of the two cited randomized controlled trials re-analyzed their data to assess partial clearance rates as well.⁶⁹

In addition to the placebo-controlled studies, Kose et al. compared the efficacy and tolerability of 3% diclofenac sodium gel to 5% imiquimod in an open-label study involving 49 patients with AKs on the scalp and face. Twenty-four patients were treated with DFS and 25 patients were treated with 5% imiquimod cream three times weekly for 12 weeks. Although the treatment duration for the DFS group is unclear, the authors reported no significant differences in investigator and patient global improvement indices between the treatment groups.⁷⁰ DFS has also been studied in combination with cryotherapy;⁷¹ in that study, complete target lesion clearance was noted in 64% of the patients treated with cryosurgery followed by DFS, and in 32% treated with cryosurgery alone.

Comments

Patients may prefer and experience fewer side effects with diclofenac when compared to 5-FU, but the duration of therapy for DFS is substantially longer than for 5-FU (90 days vs 4 weeks), but comparable to traditional 5% imiquimod schedules (16 weeks), and based on a Smith et al. study, the majority of patients are satisfied with 5-FU treatment despite experiencing more side effects.³⁹ Based on the three RCTs reviewed above, which show consistent results, and the meta-analysis of the RCTs, twice daily application of 3% diclofenac in 2.5% hyaluronan gel for 60-90 days has a SORT rating of A and certainly has a role in the management of AKs. Total treatment durations of less than 60 days (particularly for 30 days only) are not supported by good quality evidence. It should be emphasized that other topical formulations are available for diclofenac, but only the “3% diclofenac in 2.5% hyaluronan gel” should be utilized for the treatment of AKs.⁷²

Photodynamic therapy

Photodynamic therapy involves the use of a photosensitizing agent (typically via topical application) followed by phototherapy. Aminolevulinic acid (ALA) and methyl aminolevulinate (MAL) are common topical agents used for photosensitization; both are not actual photosensitizers, but protoporphyrin IX precursors.⁷⁷⁻⁷⁹ Prior to the application of ALA or MAL, pretreatment of affected areas is typically performed to allow for better absorption of either product. Pretreatment can be accomplished with gentle curettage or a number of different topical products.⁷⁹ In the U.S., ALA was approved for use in 1999 and MAL was approved in 2004.²⁴ ALA is available in the U.S. as an applicator with a 20% ALA solution.⁷⁷ MAL is available in the U.S. as a 16.8% cream,⁷⁸ the same

as MAL 160 mg/g available in parts of Europe.⁸⁰ The application of the topical photosensitizing agent is followed by an incubation period of hours, depending on the specific product. The area is wiped or rinsed off prior to exposure to the light source. A variety of light sources that emit light in the visible spectrum (400-700 nm) can then be used.⁸¹ Blue light sources, red light sources, intense pulsed light, and pulse-dye lasers are more commonly utilized.⁷⁹

Ultimately, PDT creates reactive oxygen intermediates in the tissue, which leads to cell death.⁸² Two PDT sessions are typically necessary to achieve a complete response.⁸² Common side effects include pain,⁸³ erythema, a burning sensation, crusting, and erosions.⁷⁹ Evidence does not support the use of topical anesthetics for pain relief.⁸³ Several randomized controlled trials and open-label trials were found examining ALA-PDT and MAL-PDT. Table 43-11 reviews ALA-PDT trials, Table 43-12 reviews MAL-PDT trials, and Table 43-13 reviews trials comparing PDT to cryotherapy.

Comments

The only randomized, investigator-blinded ALA-PDT trial utilized blue light,⁸⁴ and the four blinded randomized controlled trials investigating MAL-PDT utilized a red light source with several different total doses.^{80,85-87} Although access may be an issue,⁸¹ PDT is an acceptable treatment option that has consistently resulted in high clearance rates. In fact, a study by Sotiriou et al. compared two treatment sessions with ALA-PDT to 5% imiquimod in short treatment courses in an intraindividual comparison study and found similarly high overall response rates at a 6-month follow-up for both therapies (65.32% for PDT, 55.65% for 5% imiquimod cream).⁸⁸ For nonhyperkeratotic lesions, treatment of facial or scalp AKs with 1-2 sessions of MAL-PDT with red light or ALA-PDT with blue light has a SORT rating of A, based on consistent clearance rates and cosmetic outcomes.

Topical retinoids

Retinoid creams investigated for the treatment of AKs include tretinoin and adapalene. Retinoids show antiproliferative effects and have been used in the management of photodamaged skin.⁹⁹ A variety of formulations of retinoids are available, but their use in AKs is off label in the United States.⁹⁹

Tretinoin has been studied alone or in combination with other modalities. As previously mentioned, Bercovitch et al. found that the combination of 5% 5-FU and tretinoin had a significantly greater response rate compared to 5% 5-FU and a control cream.⁴³

Kligman et al. reported on three different studies evaluating the effectiveness of various strengths of

TABLE 43-11—Clinical Studies Evaluating ALA-PDT in the Treatment of AKs

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Tschen et al., 2006 ⁸⁹	Open-label, phase IV study evaluating ALA-PDT for the treatment of patients with 6-12 nonhyperkeratotic AK lesions on the face or scalp	2	ALA-PDT	Application of 20% ALA solution as double coat, incubation period of 14-18 hours, followed by PDT blue light (10 J/cm ²); retreatment of remaining target lesions at month 2	110	Percentage of target lesions cleared after two months (prior to second treatment): 72% (476/661)	12 months	At 12 months from the initial treatment, 39.8% of patients had 100% of the lesions cleared; 78.3% of lesions were clear at 12 months (458/585)
Piacquadio et al., 2004 ⁸⁴	Investigator-blinded, RCT evaluating 20% ALA with blue light vs vehicle with PDT in the treatment of patients with 4-15 nonhyperkeratotic discrete target lesions on the face or scalp	1	Vehicle-PDT	Vehicle applied to lesions twice followed by PDT blue light (10 mW/cm ²) as one treatment, with retreatment of any remaining target lesions at week 8	62	Complete response rates at week 12: 8% (4/52)	12 weeks after first treatment	Treatment with ALA-PDT resulted in a significantly greater complete response rate at week 8 and week 12 evaluations, when compared with the vehicle-PDT control
Alexiades-Armenakas et al., 2003 ⁹⁰	Prospective, randomized study evaluating 20% ALA-PDT with LP PDL compared to LP PDL in the treatment of patients with AKs on the head, extremity, and trunk (including hyperkeratotic lesions)	1	LP PDL	Single treatment with PDL (595 nm, 4-7.5 J/cm ²)	5	Mean % of head lesions cleared at 8 months: no decrease in lesions noted Mean % of extremity lesions cleared at 8 months: no decrease in lesions noted Mean % of trunk lesions cleared at 4 months: no decrease in lesions noted Mean % of head lesions cleared at 8 months: 90.32%	8 months	ALA + LP PDL are effective at reducing lesion counts with good cosmesis; no difference noted between 3-hr and 14-18 hr incubation periods.
			ALA-PDT with LP PDL	Single treatment application of 20% ALA for 3 hours or 14-18 hours followed by PDL (595 nm, 4-7.5 J/cm ²)	36	Mean % of extremity lesions cleared at 8 months: 100% Mean % of trunk lesions cleared at 4 months: 65%		

(Continued)

TABLE 43-11 Clinical Studies Evaluating ALA-PDT in the Treatment of AKs (*Continued*)

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Jeffes et al., 1997 ⁹¹	Non-blinded study evaluating 0%, 10%, 20%, and 30% ALA followed by argon pumped dye laser in the treatment of patients with 6 AKs on the face, scalp, trunk, or extremities (including hyperkeratotic lesions)	2	0% ALA-PDT	Application of 0% ALA for 3 hours, followed by argon pumped dye laser (of varying intensity)	40	Lesion complete response rates (clear of lesion) on face and scalp, 8 weeks post-treatment: 0% (0/13) Lesion complete response rates (clear of lesion) on trunk and extremities, 8 weeks post-treatment: 6% (1/16) Lesion complete response rates (clear of lesion) on face and scalp, 8 weeks post-treatment: 61% (8/13) Lesion complete response rates (clear of lesion) on trunk and extremities, 8 weeks post-treatment: 30% (7/23) Lesion complete response rates (clear of lesion) on face and scalp, 8 weeks post-treatment: 78% (24/31) Lesion complete response rates (clear of lesion) on trunk and extremities, 8 weeks post-treatment: 38% (26/69) Lesion complete response rates (clear of lesion) on face and scalp, 8 weeks post-treatment: 91% (10/11) Lesion complete response rates (clear of lesion) on trunk and extremities, 8 weeks post-treatment: 45% (9/20)	16 weeks after PDT	At the 8-week follow-up, for 30% ALA-PDT, 91% of the lesions had cleared on the face and scalp, compared to 45% of lesions on the trunk and extremities; response on face and scalp significantly better than response on extremities.
			10% ALA-PDT	Application of 10% ALA for 3 hours, followed by argon pumped dye laser (of varying intensity)				
			20% ALA-PDT	Application of 20% ALA for 3 hours, followed by argon pumped dye laser (of varying intensity)				
			30% ALA-PDT	Application of 30% ALA for 3 hours, followed by argon pumped dye laser (of varying intensity)				

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported).

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported). AK, actinic keratosis; FU, follow-up; ALA, aminolevulinic acid; LP PDI, Long pulsed pulsed-dye laser.

TABLE 43-12 — Clinical Studies Evaluating MAL-PDT in the Treatment of AKs

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N [#]	Select outcome measures	F/U	Comments/Conclusions
Wiegell et al., 2009 ⁹²	DB, RCT evaluating 16% vs 8% MAL with home-based daylight exposure in the treatment of patients with AKs of the face or scalp	1	MAL-PDT (daylight exposure) MAL-PDT (daylight exposure)	16% MAL followed by daylight exposure 8% MAL followed by daylight exposure	30	Complete response rate after 3 months: 76.9% Complete response rate after 3 months: 79.5%	3 months	No difference in response rates between different concentrations
Szeimies et al., 2009 ⁸⁰	DB, RCT evaluating 160 mg/g MAL-PDT vs placebo-PDT in the treatment of patients with AKs on the face or scalp (no randomization at one study center)	1	Placebo PDT	Application of placebo cream for 3 hours, followed by noncoherent red light, repeated 1 week later	58	Lesion response rate: 28.7% (119/414) Patient complete response rate (patients with 100% complete response): 6.9% (4/58)	3 months after last treatment	MAL PDT produced significantly greater lesion response rates and patient complete response rates when compared to placebo; 68.4% of patient had 100% clearance 3 months after their last treatment.
Braathen et al., 2009 ⁹³	Randomized, open-label study evaluating variable MAL cream concentration (160 mg/g or 80 mg/g) and variable incubation time (1 or 3 hours) in the treatment of patients with up to 4 AK lesions per treatment area on the face/scalp, trunk/neck, and extremity.	2	80 mg/g MAL-PDT 80 mg/g MAL-PDT 160 mg/g MAL-PDT 160 mg/g MAL-PDT	MAL 80 mg/g applied for 1 hour followed by red light (570–670 nm, 75 J/cm ²) with remaining lesions at 2–3 months treated a second time MAL 80 mg/g applied for 3 hours followed by red light (570–670 nm, 75 J/cm ²) with remaining lesions at 2–3 months treated a second time MAL 160 mg/g applied for 1 hour followed by red light (570–670 nm, 75 J/cm ²) with remaining lesions at 2–3 months treated a second time MAL 160 mg/g applied for 3 hours followed by red light (570–670 nm, 75 J/cm ²) with remaining lesions at 2–3 months treated a second time	25 29 28 30	Overall lesion complete response rate (after 1 or 2 sessions): 74% Overall lesion complete response rate (after 1 or 2 sessions): 77% Overall lesion complete response rate (after 1 or 2 sessions): 78% Overall lesion complete response rate (after 1 or 2 sessions): 85%	3–12 months	Overall response highest using 160 mg/g MAL with 3-hr incubation; overall recurrence rates lowest using 160 mg/g MAL with 3-hr incubation; 1-hr incubation may be sufficient in certain cases
Pariser et al., 2008 ⁸⁶	DB, RCT evaluating 16.8% MAL-PDT using red light-emitting diode light vs vehicle-PDT in the treatment of patients with 4–10 nonhyperkeratotic AKs on the face and scalp	1	Vehicle-PDT (red LED light, 630 nm, 37 J/cm ²) 16.8% MAL-PDT (red LED light, 630 nm, 37 J/cm ²)	Vehicle cream applied for 3 hours followed by red LED light (630 nm, light dose 37 J/cm ²); repeat treatment 1 week later 16.8% MAL cream applied for 3 hours followed by red LED light (630 nm, light dose 37 J/cm ²); repeat treatment 1 week later	47 49	Lesion complete response rate: 52.2% (188/360) Lesion complete response rate: 86.2% (313/363)	3 months after last treatment	MAL-PDT produced significantly greater lesion complete response rates than the vehicle-PDT control

(Continued)

TABLE 43-12—Clinical Studies Evaluating MAL-PDT in the Treatment of AKs (*Continued*)

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Babilas et al., 2007 ⁹⁴	Prospective, randomized, split-face study evaluating MAL-PDT with LED vs and MAL-PDT with VPL (IPL) in the treatment of patients with mild to moderate AKs on the forehead or scalp	2	MAL-PDT (LED, 37 J/cm ²) MAL-PDT (VPL, 80 J/cm ²)	MAL 16% applied for 3 hours, followed by LED (37 J/cm ²) irradiation MAL 16% applied for 3 hours, followed by VPL (80 J/cm ²) irradiation	25	Overall lesion complete response rate 3 months post-treatment: 56.7% Overall lesion complete response rate 3 months post-treatment: 46.6%	3 months after treatment	Pain experienced during and after therapy with VPL significantly lower than with LED; no difference in patient satisfaction or infiltration and keratosis score
Tarstedt et al., 2005 ⁹⁵	Prospective, randomized study evaluating single vs two treatments with MAL-PDT in the treatment of patients with up to 10 AKs on the face and/or scalp	2	MAL-PDT (red LED light)	160 mg/g MAL applied for 3 hours, followed by red light LED (37 J/cm ²) 160 mg/g MAL applied for 3 hours, followed by red light LED (37 J/cm ²), with retreatment at 3 months if no complete response MAL-PDT (red LED light)	105	Response rate for thin lesions: 93% Response rate for thick lesions: 70% Response rate for thin lesions: 97% Response rate for thick lesions: 88% Response rate for thin lesions: 89% Response rate for thick lesions: 84%	3 months after last treatment	In thin AKs, a single treatment with MAL-PDT is as effective as two treatments (one week apart); for thicker AKs, two treatments may be more appropriate
Pariser et al., 2003 ⁸⁵	DB, RCT evaluating MAL-PDT vs vehicle-PDT in the treatment of patients with 4-10 AKs on the face and scalp	1	Vehicle-PDT	Placebo cream applied for 3 hours followed by noncoherent red light illumination (570-670 nm, light dose 75 J/cm ²); repeat treatment 1 week later 160 mg/g MAL-PDT (noncoherent red light, 570-670 nm, light dose 75 J/cm ²)	38	Complete response rate at 3 months: 8/38 (21%)	3 months after last treatment	MAL-PDT produced significantly greater complete responses when compared with a placebo-PDT control and is effective at treating AKs

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported).

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported). AK, actinic keratosis; FU, follow-up; ALA, aminolevulinic acid; MAL, methyl aminolevulinic acid; LP PDT, long pulsed pulsed-dye laser; VPL, variable pulsed light.

TABLE 43-13—Clinical Studies Comparing PDT and Cryotherapy

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Kaufmann et al. 2008 ³⁶	Randomized, open-label controlled, intraindividual (right-left) comparison study evaluating MAL-PDT vs cryotherapy in the treatment of patients with nonhyperkeratotic AKs on the trunk, neck, and extremities	2	160 mg/g MAL-PDT	Application of 160 mg/g MAL for 3 hours followed by narrow-band red light LED (~630 nm, light dose 37 J/cm ²) at baseline, with retreatment at 12 weeks if noncomplete response noted; treatment side 1 of body	121	Mean percentage reduction at week 24: 78%	24 weeks	Cryotherapy demonstrated a significantly greater mean percentage reduction at a week 24 follow-up visit when compared to MAL-PDT.
Morton et al. 2006 ³⁷	Randomized, open-label, controlled, intraindividual (right-left) comparison study evaluating MAL-PDT vs cryotherapy in the treatment of patients with nonhyperkeratotic AKs on face and/or scalp	2	160 mg/g MAL-PDT	Double freeze-thaw cryotherapy (with 1-2 mm frozen rim around lesion) at baseline, with retreatment at 12 weeks if noncomplete response noted; treatment side 2 of body	119	Mean percentage reduction at week 24: 89.1%	24 weeks	No significant difference between cryotherapy and MAL-PDT in mean percentage reduction of face/scalp AK lesions at 24 weeks

(Continued)

TABLE 43-13—Clinical Studies Comparing PDT and Cryotherapy (Continued)

Source	Study details	Level of evidence	Treatment modality	Treatment regimen*	N†	Select outcome measures	F/U	Comments/Conclusions
Freeman et al. 2003 ⁸⁷	DB, placebo-controlled, RCT evaluating MAL-PDT vs cryotherapy vs placebo-PDT in the treatment of patients with AKs on the face or scalp (double-blind comparing active-PDT to placebo-PDT)	1	Placebo-PDT	Application of placebo for 3 hrs, followed by PDT with red light (total dose of 75 J/cm ²) at baseline, then repeated 7 days after the first treatment	23	Overall lesion response rate (complete clinical response) 3 months post-treatment: 30% (18/61) Cosmetic outcome graded as excellent by investigator: n/a	3 months	Two treatments with MAL-PDT resulted in a significantly greater lesion response than both cryotherapy and placebo
			MAL-PDT	Application of MAL 160 mg/g for 3 hrs, followed by PDT with red light (total dose of 75 J/cm ²) at baseline, then repeated 7 days after the first treatment	88	Overall lesion response rate (complete clinical response) 3 months post-treatment: 91% (267/295) Cosmetic outcome graded as excellent by investigator: 83%		
			Cryotherapy	Single timed freeze-thaw cycle with 1-2 mm rim of frozen tissue around lesion (lesions <10 mm had mean freeze time of 0:12 ± 0:13 s for lesions 10-20 mm had 0:16 ± 0:15 s freeze, and lesions >20 mm had 0:26 ± 0:11 s freeze)	89	Overall lesion response rate (complete clinical response) 3 months post-treatment: 68% (278/407) Cosmetic outcome graded as excellent by investigator: 51%		
Szeimies et al. 2002 ⁹⁸	Open, RCT evaluating MAL-PDT vs cryotherapy in the treatment of patients with up to 10 AK lesions on the face, scalp, or other location	2	160 mg/g MAL-PDT	Application of 160 mg/g MAL for 3 hrs, followed by PDT with red light (total dose of 75 J/cm ²) at baseline, then repeated 1 week later for lesions not on the face or scalp.	102	Overall lesion complete response rate 3 months after initial treatment: 68.7% (252/367) Cosmetic outcome graded as excellent or good (in patients with ≥75% lesions that had complete response): 96.3% (52/54)	3 months	Overall complete response rate was higher in the cryotherapy treated group; investigator-and patient-rated cosmetic outcomes were higher for MAL-PDT; 26% of cryotherapy group reported local adverse reactions compared to 43% in MAL-PDT group.
			Cryotherapy	Two cycles of cryotherapy during single treatment session, with 1-2 mm rim of frozen tissue around lesion	100	Overall lesion complete response rate 3 months after initial treatment: 75.3% (250/332) Cosmetic outcome graded as excellent or good (in patients with ≥75% lesions that had complete response): 80.9% (55/68)		

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported).

†N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported). AK, actinic keratosis; FU, follow-up; ALA, methyl aminolevulinate; LED, light-emitting diode; LP, pulsed-dye laser.

tretinoin creams. The first study was a double-blind study, that followed 138 patients treated with 0.05% tretinoin cream nightly for 3 months and found no change in the number or size of the AKs. The study had an open, uncontrolled extension utilizing the same 0.05% tretinoin cream for durations up to 15 months and showed a greater percentage reduction in lesions at 16 months (approximately 50%) compared to 10 months (approximately 10%), which was a significant decline when compared to baseline. A second study was conducted that was double-blind and evaluated tretinoin 0.05% cream versus a vehicle control in a parallel fashion (266 subjects assigned to tretinoin, 261 assigned to vehicle); creams were applied twice daily. No statistically significant difference was noted between the treatment groups when comparing the mean decrease in the number of lesions. In a third study, the concentration of tretinoin was increased to 0.1%, and again evaluated over 6 months, with the same protocol used from the second study: 203 patients completed 6 months of tretinoin treatment, while 207 patients completed 6 months of vehicle application. A 55% reduction from baseline in the AK count was noted in the tretinoin group, while a 41% reduction was noted in the vehicle group, a difference that was statistically significant.¹⁰⁰

Surprisingly, in the Veterans Affairs Topical Tretinoin Chemoprevention Trial (VATTC) there was an excessive number of deaths in the treatment group that received 0.1% tretinoin cream twice daily to the face and ears (compared to the vehicle control cream). After an extensive discussion regarding potential explanations for the excessive mortality, the authors concluded that it was unlikely that the excess deaths in the tretinoin-treated group are attributable to the medication.¹⁰¹

Comments

The role of topical retinoids in the treatment of AKs is still unclear. The recent VATTC trial data will likely dissuade some practitioners from using 0.1% tretinoin cream for facial AKs, but more evidence is needed to establish any causal relationship to an increase in mortality. For the treatment of AKs, the use of adapalene gel once to twice daily for 9 months has a strength of recommendation of B because only one good-quality randomized controlled trial was found. The role of tretinoin cream in the management of AKs remains unclear.

Salicylic acid ointment

Swinehart studied the use of a methyl salicylate-buffered, croton oil-containing 50% salicylic acid ointment peel in the treatment of actinic damage of the hands and forearms and reported successful results in 11 patients (with removal of ≥90% cutaneous lesions, which may have included seborrheic keratoses, actinic keratoses, and lentigines), but

did not specify the follow-up period¹⁰⁵ and was graded as a level 3 in terms of study quality.

Comments

The use of salicylic acid ointment in the treatment of AKs has a SORT rating of C, because its use is based on a case series for the study of treatment.

Oral retinoids

Two studies were found that addressed the role of the oral retinoid etretinate in the treatment or prevention of actinic keratoses;^{106,107} however, etretinate is no longer available in the U.S. market.²⁴ The first study, by Moriarty et al. reported a complete or partial response in 37/44 patients treated with etretinate and only 2/42 treated with placebo.¹⁰⁶ The second study, authored by Watson in 1986, suggested that etretinate may serve a preventive role in the management of AKs.¹⁰⁷

One study was found that addressed the role of oral isotretinoin in combination with topical 5-FU. That study, conducted by Sander et al. followed 27 patients with widespread AKs who were treated with 5% 5-FU twice daily and oral isotretinoin, 20 mg daily, with a median treatment duration of 21 days, and median follow-up of 12 months: 22/27 subjects had complete regression of palpable AKs. The authors suggested that the treatment regimen was effective at rapidly eliminating thick AKs.¹⁰⁸

Acitretin for the prevention of skin cancer has also been studied in transplantation recipients. McNamara et al. followed five heart transplant recipients on acitretin for the prophylaxis of cutaneous malignancies. Although no specific outcome measures were discussed, it was noted that actinic keratoses were resolving during the treatment period.¹⁰⁹ In a larger double-blind, placebo-controlled study of kidney transplant recipients, Bavinck et al. prescribed acitretin 30 mg daily for 6 months. Nine of the 19 patients receiving placebo developed 18 new skin cancers (15 SCC, 1 SCC in situ, 2 BCC), compared to 2 of 19 patients treated with acitretin who developed SCC; patients treated with acitretin also experienced a reduction in keratotic skin lesions (common warts, flat warts, solar keratoses), although substantial relapses were noted after treatment (Table 43-14).¹¹⁰

Comments

The evidence for the use of oral retinoids approved in the U.S. in the treatment of AKs is based mainly on case reports; more evidence is needed before oral retinoids are recommended on a routine basis, particularly for those individuals who have not undergone any organ transplantation procedures and are not immunosuppressed (and at greater risk of developing cutaneous SCC¹¹¹). Thus, the use of oral retinoids for the treatment of AKs has a C strength

TABLE 43-14—Clinical Studies Evaluating Retinoid Cream Studies

Source	Study details	Level of evidence	Treatment modality	Treatment regimen	N [†]	Select outcome measures	Comments/Conclusions
Kang et al., 2003 ¹⁰²	Investigator-masked, RCT, parallel group study evaluating 0.1% and 0.3% adapalene gel vs vehicle in the treatment of patients with 5-25 AK lesions on the face above the jawline, ears, scalp; arms and dorsum of hands	1	Vehicle gel Adapalene gel 0.1% Adapalene gel 0.3%	Once daily for 9 months Once to twice daily for 9 months Once to twice daily for 9 months	30 30 30	Mean reduction in AK number after 9 mo of therapy: 1.5 ± 1.3 (increase) Percentage of patients with clear, marked, or moderate improvement in AKs: 34% Mean reduction in AK number after 9 mo of therapy: 0.5 ± 0.9 Percentage of patients with clear, marked, or moderate improvement in AKs: 62% Mean reduction in AK number after 9 mo of therapy: 2.5 ± 0.9 Percentage of patients with clear, marked, or moderate improvement in AKs: 66%	Topical application of adapalene improved AKs and was well tolerated; no mention of complete clearance for any patient
Misiewicz et al., 1991 ¹⁰³	DB, randomized, within patient (split-face) comparative study evaluating arabinoid methyl sulfone vs tretinoin in the treatment of patients with AK lesions on the face	1	0.05% arabinoid methyl sulfone 0.05% tretinoin	Twice daily for 16 weeks Twice daily for 16 weeks	25	Mean percent decrease in the number of AKs: $37.8 \pm 6.5\%$ Mean percent decrease in the number of AKs: $30.3 \pm 9.9\%$	No significant difference between tretinoin and arabinoid methyl sulfone when evaluating the mean percent decrease in the number of AKs; both compounds are effective in treating AKs
Bollag et al., 1970 ¹⁰⁴	Clinical trial evaluating 0.1% and 0.3% retinoic acid creams in the treatment of patients with AK lesions on the face, hands, and forearms	2-3	0.1% retinoic acid 0.1% retinoic acid 0.3% retinoic acid 0.3% retinoic acid	Twice daily for 3-8 weeks on the face Twice daily for 3-8 weeks on the hands and forearms Twice daily for 3-8 weeks on the face Twice daily for 3-8 weeks on the hands and forearms	20 6 31 3	Complete regression, number of patients: 7 Reduction for more than 50%, number of patients: 8 Complete regression, number of patients: 0 Reduction for more than 50%, number of patients: 4 Complete regression, number of patients: 17 Reduction for more than 50%, number of patients: 12 Complete regression, number of patients: 0 Reduction for more than 50%, number of patients: 3	Actinic keratoses on the face responded more to retinoic acid than AKs on the hands and forearms; a higher rate of response on the face was noted in the 0.3% treated group compared to the 0.1% treated group. Of the 51 patients with facial AKs, 24 had complete clearance and 20 had reduction of more than 50%, while in 7 patients no effect was seen.

*Treatment regimen represents the prescribed treatment regimen and may not necessarily represent the actual regimen completed (unless "actual" reported)

[†]N represents the initial number of participants in each arm of the study and does not necessarily represent the number of participants who completed the study (unless "actual" reported)

AK, actinic keratosis; DB, double-blind; RCT, randomized controlled trial; F/U, follow-up.

or recommendation rating, as there is limited evidence to support the use of oral retinoids for the management of AK lesions other than in special circumstances (etretinate in organ transplant recipients).

Chemical peels

Glycolic acid, trichloroacetic acid, and Jessner's solution are examples of agents used for chemical peels. Jessner's solution is resorcinol, salicylic acid, and lactic acid.¹¹²

Tse et al. performed a split-face study in which 13 patients with AKs treated the right side of their faces with 70% glycolic acid and 35% trichloroacetic acid (GA-TCA) and the left side of their face with Jessner's solution and 35% TCA (JS-TCA). Patients were treated with 0.05% tretinoin cream for two weeks prior to treatment, and tretinoin was resumed 30 days post-treatment. Three independent evaluators utilized a clinical improvement scale to measure outcomes (0 = no response, 1 = fair, 2 = good, 3 = excellent) for AKs and several other dermatologic conditions, such as actinic lentigines. The clinical response score for AKs treated with GA-TCA was 1.58 (fair to good clinical response), and was slightly higher than the 1.33 score for AKs treated with JS-TCA (fair clinical response). Tse et al. concluded that the GA-TCA peel was an effective medium-depth peel for the treatment of photodamaged skin, not specifically AKs.¹¹² The outcome measures used in this study limit the study conclusions.

Witheiler et al. evaluated the long-term efficacy of JS-TCA compared to 5% 5-FU, also in a split-face study. Fifteen patients applied JS-TCA once to the left side of their face and 5% 5-FU cream twice daily for 3 weeks to the right side of their face, with 8 patients available for follow-up at 32 months. At a 12-month follow-up visit, a 78% and 79% reduction in the number of AKs was noted on the left and right sides of the face, respectively (JS-TCA-treated side and the 5-FU treated side, respectively). However, at the 32-month follow-up visit, a substantial increase in the number of lesions was noted for both treatment groups (with certain patients being affected more than others).¹¹³

Comments

Chemical peels, namely TCA, GA-TCA, and JS-TCA, have all been shown to be effective in reducing AK lesion counts. The use of a 30% trichloroacetic acid peel for the treatment of AKs has a SORT rating of B. The Hantash et al. study mentioned in the 5-FU section deserves further mention because of the more useful outcome measures reported. In that study, a TCA peel was compared with 5-FU and carbon dioxide laser resurfacing, and it resulted in a considerable reduction in the number of AKs at a 3-month follow-up (89.0%) and a reduced incidence of NMSC compared to placebo.²³

What is the evidence behind the use of nonpharmacologic therapies?

Cryotherapy/cryosurgery (liquid nitrogen freezing)

Cryotherapy, or cryosurgery, uses liquid nitrogen to induce tissue injury by a freezing mechanism. The freezing and thawing are both felt to play a role in tissue injury.¹¹⁴ The liquid nitrogen can be applied to the skin lesion or surface using a cotton-tipped applicator or by using a handheld spray device.

Lubritz et al. reported a 98.8% cure rate when cryotherapy was used on 70 patients with 1018 lesions (thaw time ranged from 20 to 45 seconds). Treated lesions had definite borders and were only included if an accurate count could be determined. Follow-up ranged from 1 to 8.5 years, with only 12 recurrences.¹¹⁵ More recent prospective data, though, revealed smaller cure rates^{98,116} and could represent variability in technique and AK lesion characteristics. Szeimies et al. prospectively evaluated the use of cryotherapy compared to PDT and found complete response rates after 3 months of 75.3%.⁹⁸ Thai et al. prospectively evaluated the use of cryotherapy in 90 patients (421 AKs) and reported a 39% complete response rate for freeze times of less than 5 seconds, a 69% complete response rate for freeze times greater than 5 seconds, and an 83% complete response rate for freeze times greater than 20 seconds,¹¹⁶ supporting the notion that variability in the practitioner technique has a substantial influence on the treatment outcomes.

An often cited criticism of cryotherapy is its inability to treat numerous lesions; extensive cryosurgery used for more extensive disease, or cryopeeling, has been cited as having fewer recurrences than 5-FU when measured at a 1-3 year follow-up interval.¹¹⁷ Chiarello (Table 43-15) reported on 373 patients with 34,604 actinic keratoses treated with cryopeeling, in which individual lesions and surrounding areas were treated with cryotherapy. At 6-12 months, a recurrence rate of 9% was noted in 167 patients. At 12-18 months, 12% of the 124 patients examined had new or recurrent lesions. Follow-up ranged from 6 months to 6.5 years.¹¹⁷ Despite the positive outcomes, anecdotally this technique is not widely used and more studies are needed prior to this treatment's being recommended.

TABLE 43-15—Summary of Chiarello Data¹¹⁷

Follow-up interval, months	Number of patients rechecked	New or recurrence rate, %
6-12	167	9
12-18	124	12
18-24	92	16
24-30	71	22
30-36	64	22
36-42	50	40

Comments

The success of cryotherapy will depend on a variety of factors, including freeze time and the extent of the treated field. For localized AK disease, cryotherapy has a strength of recommendation of A. Ease of use, efficacy, and versatility help maintain cryotherapy as an effective treatment choice for AKs.

Surgery (surgical excision or curettage)

Despite their being cited as a mainstay of therapy in the management of AKs¹¹⁸ and a common form of therapy,¹¹⁹ no patient-centered studies were found that evaluated curettage or surgical excision. It is unclear how frequently curettage is actually performed for AKs. Even though “other local excision or destruction of lesion or tissue of skin and subcutaneous tissue” was performed at 75.3% of all visits for AKs from 1993-1994 according to Feldman et al.² it is not clear which specific procedures were used when that term was referenced; the majority of those procedures could have been cryosurgery and not curettage. Furthermore, surgical excision or biopsy is performed when the nature of the lesion is unclear and suspicious for more invasive disease or other NMSCs and is not considered a treatment for an AK.

Comments

Curettage is generally thought to be appropriate for hypertrophic AKs and isolated lesions refractory to other treatments, and it is also helpful when the exact nature of the lesion is in question, because a histologic specimen may be submitted (but it may not be the ideal method for evaluating the histology).¹²⁰ Superficial curettage is also used before other therapies, such as PDT or cryotherapy.⁹⁸ Because the majority of the literature that discusses curettage and excisional surgery is based on opinion and perhaps usual practice, the strength of recommendation rating for curettage in the treatment of actinic keratoses is C.

Lasers

Two RCTs were found, one evaluating the use of a CO₂ laser and the other an Er:YAG laser. Ostertag et al. compared 5-FU to Er:YAG laser resurfacing and found no statistically significant difference in the mean decrease in AK numbers per patient between the two treatment groups; treatment with the Er:YAG laser resulted in a significantly greater difference in the mean percentage of lesions cleared per patient when compared to 5-FU (mean percentage of lesions cleared per patient at 6 months and 12 months post-treatment: 94.4% and 91.1%, respectively).⁴⁰ The efficacy of the Er:YAG laser has been supported by smaller cohort studies as well.^{121,122}

Hantash et al. evaluated the role of carbon dioxide laser resurfacing for AK treatment and skin cancer prophylaxis; patients treated with CO₂ laser resurfacing demonstrated a considerable reduction in the number of AKs at 3-month follow-up (92.0%) and a significantly lower cancer incidence when compared to a control group.²³ Trimas et al. used a CO₂ laser to treat 14 patients with AKs and SCC in situ disease of the face, with a follow-up range of 6-24 months, and noted no clinical evidence of disease post-treatment.¹²³ The long-term efficacy of CO₂ laser resurfacing was evaluated by Sherry et al. who reported on 31 patients with AKs treated with CO₂ laser resurfacing. Fifty-eight percent (18/31) of patients had no evidence of AKs at their follow-up visits. The mean time to recurrence in the 13 patients with recurrent disease was 23.2 months.¹²⁴

Comments

The use of laser resurfacing (Er:YAG or CO₂) for the treatment of AKs has a SORT rating of B, because each modality has at least one RCT supporting its use.

Dermabrasion

Several studies have evaluated the effects of dermabrasion on the prophylaxis and treatment of AKs. Coleman et al. followed patients for 1-5 years after being treated with dermabrasion for refractory AKs.¹²⁵ At a 2-year follow-up, 19/23 (83%) patients had no reappearance of AKs, while at a 5-year follow-up, 7/13 (54%) had no reappearance of any AKs. The study concluded that dermabrasion may play a role in the treatment of patients with severe disease who need frequent treatments. Winton et al. studied dermabrasion for scalp actinic damage in 5 patients and reported complete clearance of actinic keratoses 6 weeks postoperatively, while citing the additional beneficial effects of reduction of dyspigmentation and telangiectasias when compared to a group of patients treated with 5-FU.¹²⁶

Comments

The long-term follow-up data for dermabrasion is promising based on the aforementioned studies, with low recurrence rates noted at 2-year follow-up; dermabrasion was also cited as an effective prophylactic measure.¹²⁵ RCTs are needed to support these smaller studies, and, until then, dermabrasion will likely play a smaller, relatively selective role in the overall management of AKs in typical physician practices. Dermabrasion for the treatment of AKs has a SORT rating of C.

CONCLUSION

The justification to treat AKs for the prevention of NMSC is supported by the current literature. Hantash et al.²³ showed a significantly lower incidence of new NMSC in patients who received either 5% 5-FU, a 30% TCA chemical

peel, or treatment with a CO₂ laser, when compared with placebo. More studies like this are needed to truly define the role of treatment, observation, and follow-up (Table 43-16).

The study by Witheiler et al.¹¹³ while small in numbers, had fairly good long-term follow-up and showed that patients treated with a topical therapy, such as a

chemical peel or 5-FU, will likely present again with additional AKs, supporting the role of follow-up for patients with AKs—especially those with significant disease noted at their visit.

5-FU, imiquimod, diclofenac, cryosurgery, and PDT are all effective at reducing the number of AK lesions and all play a role in AK management. Chemical peels, lasers,

TABLE 43-16—Summary of Actinic Keratosis Treatments and Strength of Recommendations*

Therapy	Recommendation	SORT rating
5-FU		
0.5% 5-FU cream	Once daily topical application for 1-4 weeks for the treatment of multiple actinic keratoses on the face/frontal scalp	A
5% 5-FU cream	Twice daily topical application for 2-4 weeks for the treatment of multiple actinic keratoses	A
Imiquimod		
3.75% imiquimod cream	Once daily for two 2-week treatment periods, separated by a 2-week period without treatment, for the treatment of multiple nonhyperkeratotic, nonhypertrophic actinic keratoses on the face/balding scalp	A
5% imiquimod cream	Once daily, 2-3 d/week, for up to 16 weeks for the treatment of multiple nonhyperkeratotic, nonhypertrophic actinic keratoses on the face/scalp	A
5% imiquimod cream	Once daily, 2-3 d/week for two courses of therapy (3-4 weeks each), for the treatment of nonhyperkeratotic, nonhypertrophic actinic keratoses on the face/scalp	B
3% Diclofenac sodium in 2.5% hyaluronan gel		
3% diclofenac sodium in 2.5% hyaluronan gel	Twice daily application for 60-90 days for the treatment of actinic keratoses on the head, neck, hands, or arms	A
PDT		
ALA-PDT	1-2 sessions 20% ALA-PDT with blue-light source for the treatment of thin to moderately thick, nonhyperkeratotic actinic keratoses on the face or scalp	A
MAL-PDT	1-2 sessions of MAL-PDT with narrowband red-light source for the treatment of thin to moderately thick, nonhyperkeratotic actinic keratoses on the face or scalp	A
Topical retinoids		
adapalene gel	Once to twice daily for 9 months for the treatment of actinic keratoses on the face, ears, scalp, arms and dorsum of hands	B
Salicylic acid		
salicylic acid cream	For the treatment of actinic keratoses on the hands and forearms	C
Oral retinoids		
etretinate	For the prevention of AKs/SCC in transplant patients	C
Chemical peels		
trichloroacetic acid, glycolic acid, or Jessner's solution	For the treatment of actinic keratoses on the face	B
Cryotherapy		
liquid nitrogen	For the localized treatment of actinic keratoses	A
Curettage		
curettage	For the treatment of hypertrophic actinic keratoses	C
Laser		
laser resurfacing (Er:YAG or CO ₂)	For the treatment of actinic keratoses on the face or scalp	B
Dermabrasion		
dermabrasion	For the treatment of refractory actinic keratoses on the face or bald scalp	C

*Unless otherwise stated, recommendations apply to immunocompetent, non-pregnant, otherwise healthy adults.

What We Know

- Some AKs will progress to NMSC and some will regress
 - It is difficult to predict which AKs will progress to NMSC and which will regress
 - Given this difficulty, treatment is generally recommended
 - If treatment is not performed, close clinical follow-up is recommended
- AK therapies with SORT A ratings include select formulations, types, and/or schedules of the following: 5-FU, imiquimod, diclofenac, PDT, cryotherapy
- AK therapies with SORT B ratings include select formulations, types, and/or schedules of the following: adapalene, lasers, and chemical peels
- Sunscreen use prevents AKs from forming and is recommended
- Many factors are considered when choosing AK therapy,¹²⁰ including patient-specific factors (location, number, thickness, patient ability to comply with treatment) and physician-specific factors (experience, training, and ability to utilize a therapy, such as dermabrasion, laser therapy, PDT, or chemical peels)
- AKs resistant to treatment should be biopsied

topical retinoids, and dermabrasion show promise in the management of AKs, but their roles are less well-defined and remain to be elucidated.

For localized or isolated lesions, cryotherapy can be considered first-line therapy. Cryotherapy is easy to perform, has few side effects, and does not depend on patient compliance for efficacy. Curettage should be reserved for thicker hyperkeratotic lesions or may be utilized prior to procedures like PDT. For treatment of widespread and/or subclinical disease (field treatment), consideration should be given to 5-FU, imiquimod, PDT, and 3% diclofenac gel. Factors that may dictate treatment include physician skill, experience, and availability of resources (laser, dermabrasion, PDT, chemical peels), specific patient characteristics (likelihood of patient compliance, patient ability to handle anticipated side effects), and the location of AK disease (periorbital vs scalp). In addition, some patients may respond to one field therapy and fail to respond to another. A biopsy is advisable when patients have failed multiple therapies, or sooner if suspicious lesions are present.

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Treatment of Basal Cell Carcinoma

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INTRODUCTION

EPIDEMIOLOGY

Basal cell carcinoma (BCC) is the most common malignant neoplasm encountered in humans; however; it is difficult to determine the absolute incidence of BCC as it is usually excluded from cancer registry statistics.^{1,2} The average risk for a Caucasian to develop BCC is 30%.³ In dark-skinned races, the incidence of BCC is 19 times less than in Caucasians.⁴ Males are affected by BCC twice as often as females.¹ Older individuals are affected more than younger individuals, as only 20% of BCCs occur in patients younger than 50 years. Rates are highest among elderly males, however, the incidence of BCC is increasing in young women.⁵

In the United States, approximately 800,000 new cases of BCC are diagnosed annually.⁶ The incidence of BCC increases as Caucasians move closer to the equator and is known to be increasing worldwide.^{7,8} Australia has the highest known BCC incidence, at 1-2% of the population per year, which correlates to a rate of 849 per 100,000 in males and 605 per 100,000 in females.^{1,4} According to one model, BCC incidence is predicted to increase in the UK until 2040.⁹

ETIOLOGY

Familial and sporadic cases of BCC occur because multiple components of the Sonic Hedge Hog (SHH) pathway become dysregulated.¹⁰ Inactivation or deletion of PTCH1 (protein patched homologue 1) occurs in approximately 30%-60% of sporadic BCCs.^{11,12} Another 10-20% of sporadic BCC cases are due to mutations in Smoothened (SMO) that cause it to become resistant to PTCH1-mediated inhibition. Therefore, SMO becomes constitutively activated.^{13,14} Together, mutations in PTCH1 or SMO account for about 90% of sporadic BCCs.¹⁰

Protein patched homologue 1 (PTCH1) normally suppresses the seven transmembrane G-protein coupled receptor SMO by keeping it sequestered in intracellular vesicles where it is inactive. Hedgehog interacting protein (HIP) is a transmembrane protein that binds SHH and prevents it from binding to PTCH1.¹⁰ When secreted

SHH protein binds to PTCH1, PTCH1 undergoes endocytosis and becomes degraded, thus losing its ability to inhibit SMO. When SHH binds to PTCH1, SMO becomes phosphorylated. SMO phosphorylation may be catalyzed by several kinases, including protein kinase A (PKA), G protein coupled receptor kinase 2 (GRK2), and casein kinase 1.^{10,15-18} SMO then translocates to the cell surface and becomes active, leading to increased GLI transcription factor family activation via freeing GLI from the fused (Fu)-suppressor of fused complex (sFu).^{10,19} Nearly 50% of BCCs are known to overexpress SHH and therefore overwhelm HIP, thus enabling more SHH to bind to PTCH1.^{20,21} Ninety percent of BCCs are known to overexpress GLI1.²¹ GLI3 can act as either a transcriptional activator or repressor, while GLI1 and GLI2 are thought to act as only transcriptional activators.¹⁹ It is believed that the Hedgehog pathway is inactive in adults, and its reactivation in the interfollicular basaloid keratinocytes, hair follicles, and sebaceous glands is what leads to the cutaneous findings of BCC.^{10,22}

Fifty percent of the sporadic cases of BCC are known to be caused by mutations in the p53 tumor suppressor gene.² UVB radiation from 290 to 320 nm is known to cause CC→TT and C→T transition mutations at dipyrimidines.² Acute intermittent sun exposure that leads to sunburns is thought to be a major risk factor for developing BCC. People with skin phototypes I and II, albinos, those exposed to x-ray therapy for acne, those with high UVR exposure as a child, and people who have ingested arsenic are at increased risk of developing BCC.²³

Nevoid basal cell carcinoma syndrome (NBCCS) is inherited in an autosomal dominant fashion.¹ The NBCCS gene is located on chromosome 9q22.3-q31. Eighty percent of NBCCS cases involve PTCH mutations leading to a shortened PTCH protein that is deficient in its ability to suppress SMO.¹⁰ Therefore, in this pathologic state, the SHH pathway becomes constitutively active, leading to increases in downstream pathway products of GLI1 and GLI2.

DIAGNOSIS

The diagnosis of BCC is made clinically and confirmed with a biopsy and by studying the histology under the microscope.



FIGURE 44-1 Clinical picture of basal cell carcinoma-1.

There are primarily five clinical types of BCC: nodular, sclerosing, superficial, pigmented, and cystic¹ (Figures 44-1 and 44-2). The most common form of BCC is the nodular subtype. It is characterized by a papule/nodule that appears translucent or “pearly” with telangiectasia.²³ The center may ulcerate or erode and can lead to crust and scale as well as bleeding.¹ This ulceration is responsible for what was formerly termed a “rodent ulcer.” Poor cohesive forces can be noted upon biopsy of a nodular BCC; and can be fully appreciated with a curette.¹ Sclerosing BCC is also known as morpheaform and tends to be white to pale yellow in color with a waxy appearance.¹ It can be flat or mildly raised, and can be mistaken for localized scleroderma.¹ Superficial BCC is clinically characterized by being round to oval shaped, with erythema and scaling often present, allowing for confusion between eczema, psoriasis, extramammary Paget’s disease, or Bowen’s disease.¹ It is less aggressive than the other clinical subtypes of BCC, and is often found on the trunk and extremities.¹ The



FIGURE 44-2 Clinical picture of basal cell carcinoma-2.

pigmented subtype of BCC contains areas of melanin that can yield a brown, blue, or black color. The lesion typically exhibits a translucent, pearly border.¹ Histologically, pigmented BCCs most commonly have a nodular pattern. Cystic BCCs are considered a variant of nodular BCCs and present as a round, smooth, cystic mass.¹

Nevoid basal cell carcinoma syndrome presents with multiple BCCs, as well as medulloblastomas, odontogenic cysts, meningiomas, ovarian fibromas, fibrosarcomas, cardiac fibromas, and rhabdomyosarcomas.¹⁰ In 50-75% of NBCCS cases, multiple small pits on the soles and palms are present.¹ Seventy-five percent of NBCCS cases have partial or complete bridging of the sella turcica.¹ There is variability in how the BCCs in NBCCS can present, with the median age of first BCC being 25¹⁰ and the median number of BCCs being eight.¹ Additionally, patients can have no BCCs, or even more than 1000.^{1,10}

Histologically, BCC consists of a solid tumor with large, oval, deep-blue staining atypical basal cells.²³ There is a peripheral palisading arrangement, with little amounts of anaplasia, small numbers of mitoses, and variable quantities of mucinous stroma.²³ There are five major histologic patterns: nodular, superficial, micronodular, infiltrative, and morpheaform. Nodular accounts for 21% of BCC histologic patterns and is typically well developed and well defined, with peripheral palisading and consisting of a rounded neoplastic mass of cells.¹ The superficial BCC accounts for approximately 21% of BCC histologic patterns. It extends from the basal layer of the epidermis with atypical buds of basal cells. The micronodular type of BCC makes up about 15% of BCC histologic patterns and is characterized by hair bulb-sized rounded tumor nodules that are well demarcated and exhibit peripheral palisading. Infiltrative BCC accounts for approximately 7% of BCC patterns. It is characterized by a jagged configuration of variably sized tumor islands. The morpheaform histologic type of BCC constitutes 1% of BCC patterns and usually demonstrates a fibrous stroma with small elongated islands that appear as strands.

RESEARCH QUESTIONS

Various aspects of basal cell carcinoma are discussed in the chapter ahead and have been summarized as an evidence-based table (Table 44-1) for an overview.

How does histology help to determine treatment type in BCC?

The choice of treatment modality for BCCs should depend on the site and size of the tumor and whether the BCC shows indolent (superficial or nodular BCC) or aggressive growth (infiltrative BCC or basosquamous carcinoma).^{24,25} The treatment of BCCs with mixed histology is based on the most aggressive variety present in the tumor.²⁴ Although

(Text continued on page 658)

TABLE 44-1—Evidence-Based Table Summarizing Various Research Questions Related to Basal Cell Carcinomas

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
How does histology help to determine treatment type in BCC?				
Smeets NW, et al., 2004 ²⁵	To evaluate the efficiency of Mohs micrographic surgery for facial BCC	Retrospective study measuring recurrence rates	1. 5-year recurrence rate for primary BCC=3.2%, recurrent BCC=6.7% 2. Factors associated with recurrence were aggressive histology, more than 4 Mohs stages, a large defect size, and recurrent BCC	2B
Bath-Hextall FJ, et al., 2007 ²⁶	Assess treatment effects of BCC	1. Search of Cochrane Central Registry of Controlled Trials, Cochrane Database of Systematic Reviews, MEDLINE (2004 to January 2006), EMBASE (2005 to January 2006), the metaRegister of Controlled Trials (February 2006) 2. Inclusion criteria: adults with one or more histologically proven, primary BCC. The primary outcome was recurrence from 3 to 5 years. The secondary outcome was early treatment failure within 6 months, measured histologically.	1. Surgery and radiotherapy are the most effective treatments 2. Surgery had the lowest failure rate 3. Cosmetic outcomes good with PDT	2A
Batra RS, et al. ³⁷	Identify the most predictive risk factors for extensive subclinical tumor spread	Retrospective analysis of 1131 Mohs micrographic surgical cases	1. Highest risk tumors were basosquamous and morphaeform on the cheek, preoperative size greater than 10 mm 2. Age<35 years old was associated with a lower risk	2A
Hendrix JD, et al. ⁴⁰	Demonstrate that infiltrative BCC have both wider and deeper tumor extensions than nodular BCC of a similar size	Retrospective analysis involving 139 cases of infiltrative BCC and 139 cases of nodular BCC treated with MMS	Infiltrative BCC is more difficult to detect and successfully remove than nodular BCC. The number of stages, tumor width, and depth of defect were all greater with infiltrative BCC in comparison to nodular BCC	3A
Ratner D, et al. ⁴¹	To determine if perineural spread of BCC is more common than 1%	Prospective evaluation of 434 patients with BCC treated by MMS	3.8% of the 434 cases demonstrated perineural invasion	2C
Whitaker IS, et al. ⁴²	Improving treatment efficacy of BCC with CO ₂ laser and photodynamic therapy	12 patients with 13 nodular BCCs involving an uncontrolled trial using both PDT with methyl aminolevulinate and Aktilite 16 LED lamp and CO ₂ laser	No recurrences during a mean follow-up period of 18.1 months	4

(Continued)

**TABLE 44-1—Evidence-Based Table Summarizing Various Research Questions Related to Basal Cell Carcinomas
(Continued)**

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
Smucler R, et al. ⁴³	Measure the effectiveness of tumor mass reduction using Er:YAG laser	Three methods: 1. PDT with ALA 2. Er:YAG laser 3. Er:YAG to reduce tumor below 2 mm then ALA PDT All 286 subjects underwent all 3 methods of treatment. Patients were interviewed and followed at 3, 6, and 12 months	Combination therapy was the most effective at 98.97%, PDT alone was 94.85%, and Er:YAG yielded only 91.75%	2B
Martin RC 2 nd ⁴⁴	Review cases of basosquamous carcinoma from 1985 to 1988 at university institution to identify prognostic factors	Prognostic factors were analyzed using a Cox regression and log rank test	Predictive factors for recurrence included male gender, positive surgical resection margins, lymphatic invasion, and perineural invasion, at $p < .01$	4
Staibano S ⁴⁷	Determine if the angiogenic rate in cutaneous BCC correlates with biologic behavior	Blood vessels were highlighted by immunocytochemical staining for FVIII-related antigen in 2201 BCCs and compared between BCC1 (more benign pathologic morphology) and BCC2 (more aggressive appearing pathologic morphology)	All BCC2 samples of this series showed a significantly higher microvessel count than did BCC1	3A
Orengo IF, et al. ⁴⁸	Determine if subtypes of BCC require more Mohs stages to achieve tumor-free margins	Retrospective study of 342 primary BCCs treated by MMS measuring histologic subtype and number of MMS stages	A higher number of Mohs stages were required for infiltrative, morpheaform, micronodular, and mixed histologic subtypes of BCC	2B
Sexton M, et al., 1990 ⁵⁰	To define histologic patterns involving 1039 cases of BCC with correlation to adequacy of surgical margins	Retrospective analysis of archives at university institution from 1987 to 1988	93.6% of nodular and 96.4% of superficial BCC can be removed via simple surgical excision. Micronodular, infiltrative, and morpheic BCC have a higher rate of positive tumor margins after excision, at 18.6%, 26.5%, and 33.3%, respectively	2B
What is the literature on metastatic BCC?				
Tavin E, et al., 1995 ⁵¹				
Snow, et al., 1995 ⁵⁴	[Implied] To add to the body of evidence demonstrating that metastatic BCC originates from large primary tumors	Case report of 5 patients with metastatic BCC	Mean diameter of primary BCC lesion was 8.7 cm. 75% of the T2-T4 tumors accounted for the metastasis	4
Martin RC 2 nd , et al., 2000 ⁵⁷	To identify prognostic factors influencing recurrence	Medical records reviewed between 1985-1988	Positive predictors of recurrence included male gender, positive surgical resection margin, lymphatic invasion, and perineural invasion ($p < .01$)	4

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
Do higher levels of 25-hydroxyvitamin D lead to an increased risk of developing BCC?	No RCTs or CCTs in the literature			
What is the role of dermoscopy and confocal microscopy in the diagnosis of BCC?				
Menzies SW, et al., 2000 ⁷⁷	To describe a simple diagnostic method for pigmented BCC cutaneous surface microscopy	142 pigmented BCCs, 142 invasive melanomas, and 142 benign pigmented lesions were photographed, excised, and histologically analyzed. A training set of images was created to develop a model and tested on an independent test set of images	A sensitivity of 97% for pigmented BCC, 93% specificity for invasive melanoma, and 92% specificity for benign pigmented skin lesions	2C
Giacomel J, et al. ⁸³	To examine the dermoscopic features of superficial BCC	Twenty-four histologically proven cases of superficial BCC. The lesions were evaluated for vascular pattern, ulceration, and "additional dermoscopic features"	All superficial BCC cases had a shiny white to red appearance and 91.7% of lesions had irregularly dispersed, short, fine telangiectasias. 70.8% of superficial BCC demonstrated multiple small surface ulcerations with red to brown to black structureless areas	2C
Scalvenzi M, et al., 2008 ⁸⁴	To improve superficial BCC diagnostic criteria for dermoscopy	Forty-two dermoscopic images were photographed and subsequently analyzed	100% of the lesions had shiny white to red areas 78.6% had erosions 66.6% had short fine telangiectasias (SFT) 16.6% had leaf-like areas 14.3% had arborizing telangiectasias 14.3% had blue-gray globules 4.7% had large blue-gray ovoid nests	2C
Demirtasoglu M, et al., 2006 ⁸⁷	To analyze dermoscopic features of BCC along with its corresponding histology and evaluate the correlation to pigmented BCCs	Thirty-two pigmented BCCs were dermoscopically evaluated and then histologically analyzed	Large gray-blue ovoid nests, multiple gray-blue globules, maple leaf arborizing telangiectasia, yellow-brown, whitish-yellow, and black-dark brown color were significantly correlated to their histologic counterparts ($p<0.05$)	2C
Maloney ME, et al., 1992 ⁸⁸	To identify the histologic subtypes of BCC that were most often associated with pigment and to determine whether this correlated with outcome after excision	1039 nonpigmented and pigmented BCCs were divided into their histologic subtypes and compared	Of the 1039 lesions, 6.7% contained pigment. 12.4% of nodular/micronodular BCCs had pigment, 7.7% of the nodular, 7.2% of the superficial, 4.0% of the micronodular, and 3.4% of the nodular/micronodular/infiltrative	2C

(Continued)

**TABLE 44-1—Evidence-Based Table Summarizing Various Research Questions Related to Basal Cell Carcinomas
(Continued)**

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
Peris K, et al. ⁹¹	To evaluate agreement using a recently proposed method	Fifty-six images of pigmented BCCs analyzed by 5 observers	Absence of a pigment network had full agreement ($k=1$). Spoke-and-wheel areas had very good agreement ($k=.85$) and arborizing vessels ($k=0.72$). Good agreement was demonstrated for ulceration ($k=0.49$) as well as multiple blue-gray globules ($k=0.41$). No agreement was determined on large blue-gray ovoid nests ($k=0.28$) and leaflike areas ($k=0.26$)	2C
Astner S, et al. ⁹²	To evaluate the clinical applicability of a fluorescent confocal laser scanning microscope (FLSM)	Forty patients, 10 controls, 30 patients with suspected nonmelanoma skin cancers	AK and BCC had common FLSM characteristics, including nuclear pleomorphism in the granular and spinous layers and increased vascularity in the superficial dermal compartment. More typical features of BCC included nesting of atypical basal cells, increased tortuosity of blood vessels, and nuclear polarization	3B
Garaeu DS, et al. ⁹⁵	To evaluate confocal fluorescence mosaics for presence or absence of BCC	45 confocal fluorescence mosaics were blindly evaluated by an experienced Mohs surgeon and an inexperienced Mohs surgeon and compared to histologic findings	BCCs were detected with a sensitivity of 96.6% and specificity of 89.2%, a positive predictive value of 93.0%, and a negative predictive value of 94.7%	2C
What is the role of Hedge Hog inhibitors in the treatment of BCC?				
Von Hoff DD, et al. ²²	Phase 1 clinical trial to determine safety and pharmacokinetics of GDC-0449	Thirty-three patients with metastatic or advanced BCC received 3 different doses	18/33 patients had an objective response	2B
Can NSAIDS be used to prevent BCC?				
Sørenson HT, et al. ¹⁰⁴	To determine if a correlation exists between NSAID use and the incidence of cancer	Data from North Jutland Prescription Database and Danish Cancer Registry, included 172,057 patients over 9-year period	1093 cases of nonmelanoma skin cancer with SIR=1.1, 05% CI=1.0-1.2	2C
Clouser MC, et al. ¹⁰⁵	To determine if a correlation exists between NSAID use and the incidence of nonmelanoma skin cancer	Cox proportional hazard models were used to analyze the time to first SCC or BCC	A protective effect was observed for patients who reported NSAID use less than the study duration (HR=.43, 95% CI=0.25-0.73).	2C

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
What is the current role of imiquimod versus fluorouracil in treatment of BCC?				
Love WE, et al., 2009 ¹¹²	To determine rates of clearance as well as adverse effects of imiquimod or fluorouracil in BCC and SCC	Medline, CANCERLIT, and Cochrane database searches for prospective, retrospective, and case studies	Imiquimod=43-100% clearance for superficial BCC, 42%-100% for nodular BCC, 56-63% for infiltrative BCC Fluorouracil=90% for superficial BCC 100% of patients using imiquimod experienced at least 1 adverse event 97% of patients using fluorouracil experienced at least 1 adverse event	2C
Gross K, et al., 2009 ¹¹³	To evaluate the efficacy, tolerability, cosmetic outcome, and patient satisfaction with 5% 5-FU for superficial BCC treatment	31 biopsy-proven superficial BCC were treated with 5% 5-FU cream 2 times per day for 12 weeks. The BCC was excised 3 weeks after the end of treatment to evaluation for histologic cure.	28/31 (90%) of the lesions were clear, with a mean time to clearance of 10.5 weeks	2C
Geisse J, et al., 2004 ¹¹⁴	To determine the efficacy and safety of 5% imiquimod cream in comparison to placebo vehicle	Phase III trial, patients received imiquimod or vehicle cream once per day 5-7 times per week. The lesion was histologically examined 12 weeks after treatment	Clearance for imiquimod 5 times per week was 75%. Clearance for imiquimod 7 times per week was 73%. Histologic clearance for 5 times per week was 82%, while for 7 times per week was 29%.	1B
Schulze HJ, et al., 2005 ¹¹⁵	To analyze the safety and clinical efficacy of imiquimod 5% cream for superficial BCC	Multicenter, randomized, parallel, vehicle-controlled, double-blind, phase III clinical trial involving 26 centers in Europe. 166 subjects with histologically confirmed superficial BCC randomly assigned to apply imiquimod or a placebo cream, once daily for 7 times per week.	Clearance was achieved in 77% of imiquimod group versus 6% in the placebo group. Histologic clearance was achieved in 80% of the imiquimod group versus 6% of the placebo group.	1B
Gollnick H, et al., 2005 ¹¹⁶	Evaluate the long-term clinical efficacy and safety of 5% imiquimod cream in the treatment of superficial BCC	Phase III open-label study. Imiquimod was applied 5 times per week for 6 weeks (182 subjects)	12-week clearance rate was 90%. 2-year clearance rate was 79.4%.	2C
Quirk C, et al., 2006 ¹¹⁷	Evaluate the long-term clinical efficacy and safety of 5% imiquimod cream in the treatment of superficial BCC	Phase III open-label study involving 169 patients. If BCC was clear at 12 weeks, subjects were then evaluated at 3, 6, 12, and 24 month follow-up	12-week clearance was 94.1% 2-year clearance rate was 82.0%	2C

(Continued)

**TABLE 44-1—Evidence-Based Table Summarizing Various Research Questions Related to Basal Cell Carcinomas
(Continued)**

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
What is the role of cryogen in management of BCCs?				
Mallon E, et al., 1996	To determine if one freeze-thaw cycle or two freeze-thaw cycles are more effective in the treatment of superficial truncal basal cell carcinomas	Subjects were randomly assigned to either one of the two treatment groups. One group received a single 30-second freeze-thaw cycle, while the other group received a double 30-second freeze-thaw cycle	The group with the double freeze-thaw cycle attained a 95.3% cure rate. The group with the single freeze-thaw cycle attained a 79.4% cure rate.	2C
How are lasers placed in the management of BCCs?				
Campolmi P, et al., 2008 ¹³¹	Evaluate the efficacy of dye laser for superficial BCC	Twenty patients with superficial BCC were treated 5 times every 20 days	Complete response in 16/20 patients. Three recurrences were reported, with a follow-up range of 12–24 months	2C
Shah SM, et al., 2009 ¹³³	To determine the effectiveness of repeated PDL treatments on superficial and nodular types of BCC	Twenty histologically proven BCCs were treated 4 times with the 595 nm PDL at 2-week intervals. The area was biopsied and analyzed for residual tumor in comparison to controls. The diameter was also measured.	(11/12) BCCs less than 1.5 cm in diameter had complete responses, compared to 16.7% of controls (2/12), $p<0.0003$	3B
What is the role of photodynamic therapy with aminolevulinic acid or methylaminolevulinate in treatment of BCC?				
Thissen MR, et al., 2000 ¹³⁹	To determine the efficacy of PDT with delta-aminolevulinic acid for nodular basal cell carcinomas using a prior debulking technique	Twenty-four nodular BCCs were treated one time with delta-aminolevulinic acid 3 weeks after a prior debulking. Three months after treatment with PDT, all BCCs were excised and histologically analyzed.	92% of the nodular BCCs showed complete response with respect to both the clinical appearance and histologic evaluation	2C
Wang, et al., 2001 ¹⁴¹	To compare the efficacy of ALA-PDT versus cryotherapy for BCC	88 lesions of superficial and nodular BCCs randomized to receive either ALA-PDT or cryosurgery using two freeze-thaw cycles	11/44 (25%) of the patients who received ALA-PDT had recurrences, while 6/39(15%) of the patients who received cryosurgery had recurrences. 30% of the PDT patients required additional treatments	2C
Haller JC, et al., 2000 ¹⁴²	To determine if a second treatment at 7 days can improve the clearance rates	Two treatments using ALA-PDT involving 26 superficial BCCs	100% of the patients had a complete response 1 month after treatment. One lesion relapsed 16 months after treatment. Median follow-up of 27 months.	2C

Investigators	Objective	Methods	Results/Conclusions	Level of evidence
Soler AM, et al., 2000 ¹⁴³	To compare the clinical as well as cosmetic outcome of superficial BCC using a laser or PDT with ALA	245 superficial BCCs. One group received PDT-ALA and the other group received laser treatment	86% of the lesions in the laser group had a complete response. 82% of the lesions in the BL group had a complete response 6 months after treatment. There was no statistical difference	2C
Oseroff AR, et al., 2005 ¹⁵⁴	To report use of wide area 5-aminolevulinic acid PDT to treat BCCs and basaloid follicular hamartomas (BFHs)	Case report, individual areas received 1-3 treatments	85%-98% clearance was achieved	4
Foley P, et al., 2005 ¹⁶²	To investigate the histologic response, tolerability, and cosmetic outcome with MAL PDT for primary nodular BCC	Multicenter, randomized, double-blind, using MAL cream or placebo cream with broad-spectrum red light and repeated 1 week later. Lesions that partially responded at 3 months were retreated. Lesions were excised at 3 and 6 months for histologic analysis	73% (55/75) of the lesions treated with MAL PDT completely responded, while 27% or 20/75 of the placebo PDT completely responded.	1B
Is Candida antigen an effective treatment for BCC?				
Aftergut et al., 2005 ¹⁶⁴	To determine the efficacy and safety of intralesional Candida antigen for treating nodular BCC	Twenty-one patients were enrolled for the randomized, open-label, placebo-controlled trial; patients had histologically proven nodular or superficial BCC with size under 2.25cm ² . Candida antigen was injected weekly for 6 weeks. The control group received saline. 4–6 weeks after the last injection, the tumor was excised and histologically analyzed	10/17 (56%) patients in the Candida group had complete clearing of their tumor. 0/3 patients in the control group had complete clearing of their BCC. The results were not statistically significant	1B
Is there an association between statin use and BCC?				
Asgari et al., 2009 ¹⁸⁶	To determine if an association exists between statin use and BCC	Using a large, integrated, health care system, 12,123 patients with a histological diagnosis of BCC were included. From pharmacy records, exposure to statins was recorded. A Cox regression was used to determine if an independent association existed between statin therapy and risk of subsequent BCC	Statin therapy was found not to be statistically significantly associated with risk of BCC	2B

surgical excision remains the preferred treatment for most BCCs because of its ease and high treatment rates, newer noninvasive therapies have emerged for selected low-risk BCC, such as photodynamic therapy (PDT), 5-fluorouracil (5-FU), and imiquimod 5% cream. These modalities have shown great cosmetic results.²⁶

Twenty-six histologic subtypes of BCCs have been described, but for practical purposes, a clustering of these subtypes is used.^{27,28} Nodular and superficial BCC are the prototypical varieties of BCC and tend to be less aggressive. Superficial BCCs (sBCC) are generally larger, appear on the trunk, and are considered a less aggressive subtype.²⁹ Morpheaform, infiltrating, and basosquamous subtypes of BCC have distinct histologic features and are often more extensive, with higher clinical risk.^{30,38} Morpheaform BCC has been associated with greater subclinical depth of extension.³¹ Also, morpheaform and infiltrating BCCs are associated with a greater rate of recurrence.^{32,33} The clinical factors contributing to an aggressive BCC have been characterized as large size, facial location, neglect/long-standing tumor, incomplete excision, histologic variants, and perineural or perivascular invasion.³⁴⁻⁴¹

In a review of literature for randomized controlled trials, the efficacy of investigated treatments was studied. The conclusions that could be drawn from these RCTs were as follows:

- Surgical excision is the gold standard of BCC treatment.
- Mohs micrographic surgery (MMS) is preferable for recurrent facial BCC or BCC with an aggressive histologic subtype.
- Surgical treatment, although commonly used for sBCC, leads to scarring and keloid formation, because the trunk is a more susceptible location for these complications. Thus, a major role for PDT, imiquimod, 5-FU, etc., can be foreseen, although more trials need to be conducted to compare the efficacies of these modalities in treatment of sBCC.
- In nodular BCC (nBCC) at low-risk anatomic sites, cryosurgery, curettage, surgical excision (SE) and radiotherapy have been tried, but more research is needed to determine if noninvasive methods should be applied in recurrent tumors. Photodynamic therapy (PDT) combined with lasers has also been tried for nodular BCCs and will be discussed subsequently.^{42,43} In the few cases where surgery is impossible or undesirable, it may be advantageous to treat a patient with a less-invasive method that may be less effective.

Tumors with perineural spread are difficult to manage because skip areas tend to complicate margin assessment.⁴⁴⁻⁴⁶ Achieving complete clearance is often unsuccessful and may result in focal neurologic deficits.

In addition, increased tumor vascularity can be correlated with aggressive cases of BCC. The increased vascularity can be assessed by a factor VIII immunohistochemical stain.⁴⁷ Perivascular invasion may lead to tumor extension

by increasing blood supply to the tumor mass and creating channels for local and distant spread.

The aggressive histologic subtypes of BCC have been found to require more Mohs surgery stages to achieve tumor-free margins, with 37% requiring three or more stages,⁴⁸ compared to an average of 1.6 stages in a large sample of histologically low-risk BCC cases.⁴⁹ Aggressive subtypes are also frequently associated with residual positive margins (21.8% of 239 cases).⁵⁰

CONCLUSION

Surgical excision is the standard of care for BCC. MMS is the best option for the treatment of aggressive BCCs, BCCs on the face, and recurrent BCCs. Nodular BCCs can be managed with SE, radiotherapy, combined ablative lasers with PDT, and cryosurgery. PDT is a useful modality for sBCC.

What is the literature on metastatic BCC?

Metastatic BCC (MBCC) is defined as primary cutaneous BCC that spreads to anatomically distant sites as histologically similar deposits of BCC. Metastasis of BCC is rare: the incidence ranges between 0.003 and 0.55%.^{51,52} Less than 300 cases of MBCC have been reported in the literature.⁵³ Metastases occur in males and females in a 2:1 ratio.^{54,55} The majority of MBCCs are from primary BCC in the head and neck region.⁵³ The most frequent site of BCC metastasis is regional lymph nodes, followed by bone, lung, and liver.⁵⁶⁻⁵⁸ Involvement of salivary glands has been reported in several patients, although it may be difficult to distinguish direct extension of tumor from true metastasis at this site.^{52,59,60}

The risk factors associated with MBCC are actinic damage, fair complexion, history of excessive sun exposure, family history of skin cancer,⁶¹⁻⁶³ middle age, male sex,⁵³ large ($>10 \text{ cm}^2$) solitary tumor,^{64,65} and a long-standing lesion.⁶⁶ The histologic patterns that are aggressive, such as basosquamous, metatypical, morpheaform, and adenocystic BCC, may determine the ability of BCC to create its own specialized stroma at the distant metastatic site.⁶⁷⁻⁶⁹ These risk factors, when present, are an indication for more aggressive initial treatment to prevent recurrence and further progression of BCC infiltration and metastasis.

In a case report by Ting et al. two cases of metastatic BCC were presented.⁶⁴ These patients were managed by local radiation therapy and palliative methods only. Patient 1 died 7 years after, and patient 2 died 2 years after, the documentation of metastases, despite aggressive treatment.

The prognosis for MBCC is poor. Estimated median survival after metastases ranges from 8 to 14 months; the longest known survival is 25 years.^{53,54}

CONCLUSION

Metastatic BCC, although a rare condition, should be considered when dealing with aggressive histology, large

solitary BCCs, prolonged photodamage, and a positive family history, especially in fair complexioned populations.

Do higher levels of 25-hydroxyvitamin D lead to an increased risk of developing BCC?

BCCs are known to express the 1,25(OH)₂D₃ vitamin D receptor (VDR). UVB radiation has the dual effect on the skin of producing both CC→TT and C→T transition mutations at dypyridines as well as increasing the synthesis of 25-OH vitamin D. Additionally, the transcription factors GLI1 and GLI2 are known to have VDR consensus sequences, which may allow for vitamin D regulation of the Sonic Hedgehog pathway.⁷⁰ 1,25(OH)₂D₃ may also play a role in assisting cells in DNA damage repair, as it has been noted that skin cells treated with 1,25(OH)₂D₃, demonstrate more photoproduct excision in both human and mouse cells as well as increased expression of XPC and DDB2/XPE.^{68,71,72} *In vitro* studies have demonstrated that vitamin D may actually inhibit BCC cell growth. More specifically and recently, Xiao et al. have shown that 5–10 µM vitamin D reduces the expression of GLI1 by a factor of 4 and therefore exhibits an effect similar to that of 10 µM cyclopamine.⁷³

Despite this evidence, there are few epidemiologic studies linking serum vitamin D levels to either promoting or inhibiting BCC formation. Certainly, the mode of attaining vitamin D plays a significant factor in the development of cutaneous carcinogenesis. At least one nested case-control study has attempted to show a link between BCC and pre-diagnostic serum vitamin D levels.⁷⁴ In fact, the investigators found that for every 1 ng mL⁻¹ rise in serum 25-OH vitamin D, there was a 3% increased risk of developing BCC.⁷² However, the authors may not have adequately controlled for acute intermittent UV exposures.⁷² In addition, and subjects who reported higher occupational UV exposure had lower serum levels of 25(OH)D.⁷²

Future studies are needed to explore the association between serum vitamin D levels and risk of BCC, with careful attention to controlling for UV radiation exposure and comparing oral supplementation of vitamin D versus UV radiation exposure.

CONCLUSION

More epidemiologic evidence will need to be gathered to affirm or refute the link between vitamin D levels and risk of developing BCC, with special attention paid to the route by which the vitamin D is attained.

What is the role of dermoscopy and confocal microscopy in diagnosis of BCC?

The early detection of BCC is helpful in guiding curative treatments, avoiding destructive growth, preventing

local spread, and eventually preventing metastases. The early clinical detection of BCCs was made more feasible and convenient with the introduction of dermoscopy and confocal microscopy.

Dermoscopy

Dermoscopy has the highest clinical impact among all noninvasive diagnostic procedures available for differentiating malignant from benign skin lesions at an early stage.^{75,76} Dermoscopy is a noninvasive diagnostic technique that permits the visualization of morphologic features that are not visible to the naked eye, thus representing a link between macroscopic clinical dermatology and microscopic dermatopathology. The dermoscopic model for the diagnosis of the pigmented variant of BCC is based on the absence of a pigmented network and the presence of at least one positive feature, including: (1) ulceration (not associated with a recent history of trauma); (2) multiple blue/gray globules; (3) leaflike areas; (4) large blue/gray ovoid nests; (5) spoke-wheel areas; and (6) arborizing (treelike) telangiectasia.⁷⁷ Yet, a wide range of clinical and dermoscopic characteristics may be presented by BCCs along with a fairly large variety of histologic patterns.^{75,78} These have been discussed in several case reports.^{79–84}

Altamura et al. conducted a retrospective analysis of 609 BCCs and 200 melanocytic and nonmelanocytic lesions and assessed inter-rater reliability of dermoscopic BCC criteria.⁸⁵ They found that classic BCC patterns, including arborizing telangiectasia, blue/gray ovoid nests, ulceration, multiple blue/gray globules, leaflike areas, and spoke-wheel areas, were significantly increased in pigmented BCCs compared with nonpigmented and heavily pigmented BCCs. Among nonclassic BCC patterns, short, fine, superficial telangiectasias and multiple small erosions were detected. Two new patterns, named “concentric structures” and “multiple in-focus blue/gray dots,” were described. Dermoscopic features suggestive of melanocytic lesions (e.g., multiple brown to black dots/globules, blue/white veil-like structures, and nonarborizing vessels) were observed in 40.6% of BCCs and were significantly increased in heavily pigmented BCCs. Expert observers provided an accurate (sensitivity: 97%) and reliable (K: 87%) dermoscopic diagnosis of BCC, although a significant difference in terms of specificity ($P = .0002$) and positive predictive value ($P = .0004$) was found. Arborizing telangiectasia, leaflike areas, and large blue/gray ovoid nests represented reliable and robust diagnostic parameters.

On the other hand, Scalvenzi et al. in their investigation on dermoscopic patterns in 42 superficial BCCs, demonstrated the presence of shiny white to red areas, short fine telangiectasias, and erosions as the chief dermoscopic criteria of superficial BCC. Scalvenzi et al. also concluded that other findings were not as strongly associated with superficial BCCs but did help in differential diagnosis from other pigmented and nonpigmented skin lesions.⁸⁶

Because of the clinical similarities between pigmented basal cell carcinomas and other melanocytic pigmented lesions, especially melanoma, dermoscopy proves to be a useful tool for the diagnosis of pigmented BCCs. There are special dermoscopic features described for pigmented BCCs, of which ulceration, large gray-blue ovoid nests, multiple gray-blue globules, maple-leaflike areas and arborizing telangiectasias were found to correlate with their histopathologic counterparts.⁸⁷ In pigmented BCCs, melanin can be found in the tumor mass or surrounding dermis histopathologically. In the tumor mass, melanin can be seen in hyperplastic melanocytes or may be taken up by surrounding tumor cells. However, in the dermis, melanin can either be found in melanophages or lie free. Melanin might also be found in hyperplastic epidermal melanocytes in the overlying epidermis.^{88–90}

Interobserver agreement is of great importance in surface microscopy. Peris et al. evaluated observers' global agreement and interobserver agreement on each dermoscopic parameter for 56 pigmented BCCs.⁹¹ Five observers, classified on the basis of their expertise, conducted this study, and the results suggested that dermoscopy is a reproducible method for ulceration, spoke-wheel areas, and arborizing telangiectasias. No agreement was reached for large blue-gray ovoid nests and leaflike areas.

Confocal Microscopy

Another noninvasive modality very useful for detecting, evaluating, and monitoring a number of cutaneous lesions is confocal microscopy. It offers high-resolution real-time imaging of human skin with a confocal microscope either *in vivo* or in freshly excised tissue *ex vivo*. Similar to conventional histology, nuclear and cellular morphology is observed in thin optical sections. Use of contrast agents, such as acridine orange in fluorescence and acetic acid in reflectance, help enhance contrast. Although histology remains the gold standard for microscopic evaluation of the skin, confocal microscopy has the advantages of being rapid and noninvasive and allows for repeated dynamic evaluations over time; it also does not cause any tissue damage or alteration by processing or staining.

In a study by Astner et al. fluorescent confocal laser scanning microscopy (FLSM) was used for diagnosis and therapeutic monitoring of nonmelanoma skin cancers (NMSCs).⁹² The BCCs showed comparable epidermal pleomorphism and characteristic nesting of atypical basal cells, and they demonstrated increased blood vessel tortuosity. FLSM was able to detect the morphologic characteristics of BCC that correlated with routine histology. To allow the noninvasive monitoring of treatment response to imiquimod, all corresponding FLSM features for superficial BCC were evaluated at baseline and variable time points during and after therapy. The preliminary observations showed an initial increase of inflammatory cells

relating to local immune response, and these findings subsided with cessation of therapy. The vascular dilatation or increased vascularization of treatment sites was observed after a course of 6 weeks of topical treatment and persisted at the 12-week follow-up, relating to the induction of neovascularization following imiquimod therapy. With FLSM, timing of the evaluation remains an important aspect, because the distribution of fluorescein follows a characteristic dynamic in live skin. Reflectance confocal microscopy (RCM) allows an evaluation without exogenous contrast agents.

Besides its use in detection and monitoring of NMSCs, confocal microscopy has been shown to be a tool to expedite Mohs surgery.^{93,94} The preparation of frozen histology is slow, requiring 20 to 45 min per excision. Confocal reflectance mosaicing may enable rapid detection of BCCs directly in surgical excisions, with minimal need for frozen histology. Soaking the excisions in acetic acid rapidly brightens nuclei and enhances BCC-to-dermis contrast, known as "acetowhitening." Mosaics created displayed up to 12 × 12 mm of tissue in Mohs surgical excisions, which corresponded to the view with twofold magnification that is routinely used by Mohs surgeons when examining frozen histology with a standard light microscope. These mosaics were created in less than 9 min, whereas preparation of frozen histology requires 20 to 45 min per excision. This suggests that large-area mosaicing may offer a means for rapid examination of BCCs directly in fresh excisions while minimizing labor and costs.

In one study, 45 confocal mosaics were blindly evaluated for the presence (or absence) of BCC tumor and the blinded evaluation was compared to the gold standard of frozen histopathology.⁹⁵ BCCs were detected with an overall sensitivity of 96.6%, specificity of 89.2%, positive predictive value of 93.0%, and negative predictive value of 94.7%, demonstrating the potential utility of confocal microscopy for rapid surgical pathology at the bedside to expedite and guide surgery.

CONCLUSION

BCCs show a large spectrum of global and local dermoscopic features; heavily pigmented BCCs show the most challenging combinations of dermoscopic features.

Confocal microscopy has emerged as a very useful modality for diagnosing and monitoring BCCs and to expedite Mohs surgery.

What is the role of Hedge Hog inhibitors in the treatment of BCC?

Several Hedge Hog inhibitors are being explored as possible therapeutic agents in the treatment of BCC. One such agent and perhaps the most well known, cyclopamine, is derived from the lily plant *Veratrum californicum*.

It binds directly to SMO's transmembrane helices and inhibits its action.⁹⁶ It is theorized that cyclopamine induces a conformation change in SMO or affects the localization of SMO, thereby inactivating it.⁹⁴ Cyclopamine has also been shown to upregulate Fas expression leading to Fas/Fas ligand interaction and caspase 8-mediated apoptosis in murine BCC cells.⁹⁷ A topical preparation of cyclopamine was studied in a Phase I clinical trial, however, the trial was discontinued because of poor transepidermal drug penetration.⁹⁸ Despite the poor transepidermal penetration, histologic clearing was noted in some patients.^{10,95} Unfortunately, cyclopamine probably should not be used in pregnant patients because it is known to cause cyclopia in the lambs of ewes that eat *Veratrum californicum*.^{10,99}

GDC-0449 is another HH inhibitor that has recently been used in a Phase I clinical trial. GDC-0449 inhibits signal transduction in the hedgehog pathway by directly binding to SMO, rendering it unable to activate downstream target genes.²² It was discovered by high-throughput screening of a small molecule library.²² GDC-0449 has been shown to be effective against other hedgehog-dependent neoplasias, such as medulloblastoma, colorectal cancer, and pancreatic carcinoma.²² One trial showed a response to GDC-0449 in 18 of 33 patients with locally advanced or metastatic BCC.²² At doses of 150 mg, 270 mg, or 540 mg per day, there were no reported dose-limiting toxic side effects or grade 5 adverse events. One patient did exhibit a grade 4 adverse event. It was noted that out of the four patients with progressive BCC (unresponsive to GDC-0449), two had increased hedgehog signaling pathway activity, suggesting an unknown mechanism behind their lack of response.²²

Other small-molecule inhibitors of SMO include SANT1-4 and G-024856. At least one phase I trial of G-024856 (formerly known as CUR61414) is ongoing.¹⁰ Williams et al. demonstrated that G-024856 decreases HH signaling involving oncogenic PTCH1 mutations.^{97,100} Chen et al. suggest that the SANT1-4 molecules may interact differently than cyclopamine with SMO, and therefore may be useful in the future to clinically target cyclopamine nonresponders.¹⁰¹ Future research will need to determine the possible clinical utility of these small molecules as well as to develop a more detailed understanding of the HH signaling pathway.

CONCLUSION

At least two Phase I clinical trials with HH inhibitors have demonstrated histologic response. The results of the trials demonstrate proof of principle from basic science to clinical trials. Further research will need to be carried out to better understand BCC at the molecular level and to account for patients who do not respond to a particular HH therapy.

Can NSAIDs be used to prevent BCC?

NSAIDs have been theorized to prevent the occurrence of NMSCs. Recent evidence demonstrating that NSAIDs may reduce the incidence of colorectal polyps and esophageal, stomach, ovarian, and breast cancers, but increase the risk of kidney, lung, and prostate cancer has stimulated research into animal model and human tumors.^{102–104} One of the most recent studies found a protective effect of non-ASA NSAIDs on the development of a first BCC.¹⁰⁵ The protective effect was only statistically significant for subjects who reported short-term use (i.e., less than the study duration, with a HR of 0.43, 95% CI 0.25–0.73).¹⁰³ In addition, the study found that more recent NSAID use was more protective than long-term use for risk of developing a first BCC.¹⁰³ The investigators suggest that this effect may be caused by receptor overexpression with alternative signaling pathways becoming more active.¹⁰³ The results of this study also suggest that NSAIDs likely block different pathways of BCCs and SCCs en route to carcinogenesis.¹⁰³ Unfortunately, as of this date, there have been no randomized prospective clinical trials examining this issue.¹⁰¹

It is hypothesized that chronic inflammation, largely through UV radiation^{106,107} exposure, leads to the release of arachidonic acid. Arachidonic acid then leads to prostaglandin synthesis, which is believed to release free oxygen radicals causing tissue damage. Prostaglandins may prevent apoptosis of UV-damaged cells, therefore leading to promotion of a possible neoplastic process.¹⁰⁸ There are three known classes of COX inhibitors. COX-1 has been found throughout human and mouse epidermis, whereas COX-2 is found predominantly in the suprabasilar keratinocytes.¹⁰⁹ Paradoxically, BCC is known to express little quantities of COX-1 or COX-2 isoenzymes.¹⁰⁷

Future studies may be aimed at the basic science level to determine possible alternative pathways via which NSAIDs may alter the pathway to carcinogenesis. In addition, more controlled prospective studies will be needed to cement the link between NSAIDs in the chemoprevention of BCC, if one actually exists.

CONCLUSION

NSAIDs have been shown to protect against BCC with short-term use. More basic science studies will need to be carried out to determine the mechanism behind this finding.

What is the current role of imiquimod versus fluorouracil in treatment of BCC?

Imiquimod is a nucleoside analogue of the imidazoquinoline family and functions as an immune response modifier that specifically acts as a toll-like receptor 7 and

8 agonist.¹¹⁰ This agonist stimulates the innate immune system to produce interferon, thereby augmenting the TH₁ immune response and hence antitumor/antiviral activity.¹¹⁰ Fluorouracil is a pyrimidine analog that inhibits DNA synthesis by blocking the methylation reaction converting deoxyuridylic acid to thymidylic acid. Therefore, thymine is not produced or is produced at lower levels, resulting in unbalanced cell growth and eventually cell death.¹¹¹ Imiquimod and fluorouracil are used in topical format for treating superficial BCCs. A recent meta-analysis reviewed different dosing regimens and long-term follow-up for treating BCC with imiquimod and fluorouracil.¹¹² When imiquimod was used daily at least 5 days per week for 6 to 12 weeks to treat superficial BCC, 81% of the patients demonstrated histologic cure at 6 or 12 weeks.¹¹⁰ One long-term study from that group showed that at 5 years after the 6-week treatment period consisting of 5 days per week of application, 69% of the patients were clinically asymptomatic.¹¹⁰ When imiquimod was used in the treatment of nodular BCC, applied daily for 12 weeks, 76% histologic clearance was observed at 6 weeks.¹¹⁰ When imiquimod was applied two times per day for 3 days per week, 42% histologic clearance was observed at 6 weeks.¹¹⁰ Imiquimod application was also explored in infiltrative BCC, yielding 5-year histologic clearance rates of 63% and 56%.¹¹⁰ Fluorouracil was applied twice daily for superficial BCC for an average of 11 weeks, with 90% histologic clearance 3 weeks after treatment.^{110,113} Unfortunately, 5-year follow-up did not occur in that study.

Imiquimod and fluorouracil exhibit a number of side effects. More specifically, application of topical 5% imiquimod cream has been shown to result in hypopigmentation (9-67% of subjects), erythema (63-100%), pruritus (16-67%), burning (6-35%), pain (3-35%), erosion (36-53%), ulceration (25-27%), flu-like symptoms (9%), scarring (15%), and crusting, scabbing, and scaling (52-65%).¹¹⁰ Interestingly, a higher level of inflammatory response predicts a higher rate of tumor clearance.¹¹⁴ The inflammatory response tends to be most intense from weeks 2 to 6 to after initiating imiquimod and is known to last up to 12 weeks, with possible scaling and erythema lasting up to 2 years.^{110,115-117} Fluorouracil is associated with erythema (33-97%), pain (33-50%), dermatitis (20%), pruritus (17%), scarring (9-16%), scabbing, crusting (13%), burning (7%), ulceration (4-9%), erosion (6%), and hyperpigmentation (3%)^{112,110}. It was noted that 97% of subjects using fluorouracil experienced at least one adverse effect.¹¹¹ Unlike imiquimod, a robust inflammatory response is not associated with higher levels of tumor clearance.¹¹⁰

Cost is another important issue when considering treatment modalities involving BCC. Assuming 1 cm superficial BCC located on the trunk, Murphy et al. calculated that topical imiquimod 5% cream for 6 weeks cost \$814.08, topical fluorouracil for 8 weeks cost \$499.96, Mohs

microsurgery cost \$535.45 for a single stage, curettage with electrodesiccation cost \$128.84, and surgical excision with intermediate layered closure cost \$415.40.¹¹⁸

Since cure rates for conventional BCC treatment modalities range from 90-99%,¹¹⁹ imiquimod and fluorouracil should remain alternatives for patients in whom conventional therapies are contraindicated or in patients with superficial BCC, given its less aggressive nature. In addition, topical fluorouracil and imiquimod are associated with a number of cutaneous side effects and may actually cost more than conventional therapy.

CONCLUSIONS

Since cure rates for conventional BCC treatment modalities range from 90 to 99%,¹²⁰ imiquimod and fluorouracil should remain alternatives for patients in whom conventional therapies are contraindicated or in patients with superficial BCC, given its less aggressive nature. In addition, topical fluorouracil and imiquimod are associated with a number of cutaneous side effects and may actually cost more than conventional therapy.

What is the role of cryogen in management of BCCs?

Cryotherapy or cold-induced destruction of nonmelanoma skin cancer can be achieved with liquid nitrogen cryosurgery. Variations in spray technique and duration and number of freeze/thaw cycles have been tried to improve results.¹²¹ This technique is most suited for treatment of low-risk primary basal cell and squamous cell carcinomas.^{122,123} In one study, the recurrence rates were similar for cryosurgery and surgical excision, and results of another study showed a higher recurrence rate for basal cell carcinoma treated with cryosurgery (39%) than for carcinoma treated with radiotherapy (4%) at 2-year follow-up.^{124,125}

Cosmetic results were similar for cryosurgery and radiotherapy, whereas results of surgical excision were better than those of cryosurgery.

CONCLUSION

With close monitoring, cryotherapy is an option used conventionally for management of less aggressive and superficial BCC.

How are lasers placed in the management of BCCs?

Due to commonly arising adverse events and complications with medical and surgical therapies, lasers have emerged as a possible and potential modality for treatment of skin cancers. Imiquimod is associated with erythema, edema,

weeping, pruritus, permanent hypopigmentation, crusting/scabbing/scaling, erosion, burning, and pain.¹¹⁰ 5-FU may cause erythema, pain, irritant dermatitis, and pruritus.¹¹⁰ Procedures like cryosurgery and curettage and electrodesiccation often lead to hyperpigmentation and atrophic scarring.¹²⁶ Surgery and radiotherapy also lead to visible scarring. Thus, lasers could offer a cosmetically good outcome for BCCs. Good candidates for lasers would be those having multiple BCCs or those who cannot tolerate surgery or the inflammation associated with topical medications. The pulsed dye laser (PDL) has been tried for BCC and works on the principle of selective photothermolysis. This indicates that the laser targets a particular chromophore within the lesion while preserving the surrounding tissue. The rationale for using PDL for BCCs is that BCCs often have telangiectasias. These may be a basket-like capillary plexus interwoven throughout the tumor bed, with many abnormal blood vessels with luminal diameters of 20 µm. By specifically targeting the tumor vasculature, BCC burden may be decreased or even eliminated with less damage to the surrounding skin and structures.

Lasers can be used in the treatment and prophylaxis of skin cancers by:

- Nonspecific ablation of dermis
- Coherent light sources in PDT
- PDL alone

The ablative approach suggests elimination of premalignant cells in the cancerization field. Studies have focused on the CO₂ and Er:YAG lasers, the role of which is discussed in the next research question.

The pulsed dye laser has been used to selectively target tumor vasculature, with success in treating glottal dysplasia and squamous cell carcinomas *in situ* using 585 nm PDL.^{127,128} Depending on fluence, 595 nm PDL can penetrate skin to thicknesses ranging from 0.75 to 1.25 mm (encompassing most BCCs).¹²⁹ Allison et al. conducted single treatment of 585 nm PDL on seven BCCs, which resulted in histologic clearance of only one tumor.¹³⁰ Campolmi et al. conducted two studies on superficial BCCs with the 595 nm PDL which demonstrated no clinical recurrences at a minimum follow-up of 1 year in 16 out of 20 BCCs.^{131,132} Repeated PDL treatments on BCCs of superficial and nodular subtypes and of varying diameters revealed that tumor histologic types among the complete responders included superficial, nodular, micronodular, and keratinizing. Incompletely responding BCCs showed a significant reduction in tumor burden after PDL treatment, with residual histologic tumor burden ranging from <1% to 29% of the original clinical tumor diameter, compared to 13–68% residual tumor burden for the corresponding controls.¹³³

In a study by Moskalik et al. on 3461 patients with 3624 facial skin cancer lesions, it was reported that Nd:YAG laser irradiation can be used for basal cell cancers of the

face, particularly if the tumors are located in the periocular region or on the eyelids.¹³⁴

Photodynamic therapy for BCCs may utilize a laser as the light source. Studies have been done with diode laser, in one of which 15 basal cell carcinoma (BCC) lesions and 19 Bowen's disease were submitted to 6-h topical and occlusive 20% 5-ALA plus DMSO and EDTA, and later were exposed to 630 nm diode laser, 100 or 300 J/cm² dose.¹³⁵ At 3 months, tumor-free rate was 91.2%, whereas at 60 months, it was 57.7% (15/26), and slightly higher in BCC (63.6%; 7/11). The relation between the reduction of the clinical response and the increase of tumor dimension observed at 18 months was lost at 60 months. The sBCC recurrence was earlier compared to the nBCC one.

CONCLUSION

Lasers have a multifaceted role in BCC treatment. They can be used alone (PDL), as the noncoherent light source for PDT, as ablative therapy managing the field of cancerization, or as an adjuvant in debulking of the tumor (as will be discussed in the next research question).

What is the role of photodynamic therapy with aminolevulinic acid or methylaminolevulinate in treatment of BCC?

Photodynamic therapy (PDT) refers to the procedure wherein a photosensitizer is first used on the skin, followed by an incubation period, allowing the uptake of the photosensitizer by the neoplastic cells, and finally is exposed to a light source (coherent or noncoherent), triggering a reaction in the cancer cells and damaging them. The photosensitizers used in the clinical trials for treating BCCs are aminolevulinic acid (ALA) and methyl-aminolevulinic acid (MAL). The photosensitizers taken up by the cells are metabolized into phototoxic compounds like protoporphyrin IX (PpIX).¹³⁶ Various light sources have been tried, including blue light, red light, and lasers.

Several studies have investigated the use of ALA-PDT for the management of BCCs with a large number of patients and the clearance rates ranged from 66–100%.^{137–141} From the many studies conducted to examine ALA-PDT for the treatment of BCCs, it may be concluded that multiple treatments most likely lead to a higher clearance rates than a single treatment.^{142,143} One of the studies involved long-term follow-up of 47 patients with 95 sBCC. The reported response rate was 44% at 36 months after therapy.¹⁴⁴ In addition, ALA-PDT may be superior to both electrosurgery for large superficial BCCs and to excision in patients with multiple BCCs.¹⁴⁵

Besides being a noninvasive treatment, the main advantages of ALA-PDT are significantly shorter healing times and excellent cosmetic results. In addition, PDT used as

field treatment instead of spot treatment, helps to treat the entire field of cancer. The concept of “field cancerization” refers to a process ‘whereby the whole neighborhood is affected’.^{146–149} It was first described by Slaughter et al. in 1953 and has been expanded to include areas that are clinically occult but have multifocal (pre)neoplastic changes and microsatellite alterations, showing genetic mutations that precede the development of second primary tumors and local recurrences.¹⁵⁰ So, treating severely photodamaged skin, which has a risk of developing more BCCs, can help treat many lesions that may not be clinically evident at present but may manifest as BCC in future.

Increased incidence of nonmelanoma skin cancers (NMSC) is known in patients with immunosuppression, such as AIDS patients,^{151,152} transplant patients, patients on immunosuppressive drugs, etc. Immunosuppression in organ transplant patients strongly contributes to the increase in skin cancer incidence—being 65–250 times more frequent than in the general population. Often these patients suffer from a second and third lesion and the severity of the tumors is linked to their number.¹⁵³ PDT has been suggested as a management tool in such patients because of destruction of subclinical lesions, induction of an antitumor response that suppresses development of new carcinomas, or both.¹⁵⁴ Given the role of innate and adaptive immunity in PDT, it is not surprising that ALA-PDT is less effective in immunosuppressed transplant recipients. Besides, there is also increasing evidence that PDT induces antitumor responses and generates tumor vaccines.^{155,156} Existing protein antigens and neoantigens produced by oxidation or by the crosslinking of adjacent membrane or cytoplasmic proteins can be bound and subsequently presented by PDT-induced stress protein chaperones, such as HSP-70.¹⁵⁷

On the other hand, one of the studies brought out the limitations of using coherent and incoherent light sources for the ALA-PDT treatment of large or multiple BCCs, namely, unacceptably long treatment of large or multiple lesions and high costs. Moreover, repetitive treatments, debulking,¹⁵⁸ and the use of penetration enhancers such as DMSO (dimethyl sulfoxide)^{159,160} have made ALA-PDT a popular treatment for superficial BCCs. Combining PDT with CO₂ or Er:YAG lasers has also been tried in nodular BCCs to achieve ablation or reducing the tumor to a depth less than 2 mm and then eradicating the remaining tumor (if any) with PDT.^{42,43} Also, greater saturation of the pathologic tissue with ALA can be achieved after surface treatment with such lasers, as it enhances the penetration of ALA.¹⁵⁶

MAL-PDT was investigated by Foley et al. in two randomized studies.¹⁶¹ They evaluated the histologic response, tolerability, and cosmetic outcome with MAL-PDT for primary nodular BCC (≤ 5 mm in depth). Two multicenter, randomized, double-blind studies with similar design and procedures were conducted. Histologically verified lesion complete response rates were higher with MAL-PDT than with placebo (73% vs. 27%). Treatment was most effective

for facial lesions. Cosmetic outcome was good or excellent in 98% of evaluable, completely responding lesions treated with MAL-PDT. MAL (Metvix in Canada and Metvixia in the U.S., Galderma) is available as a cream, while ALA is available in a stick form (Levulan Kerastick, Dusa Pharmaceuticals Inc., Wilmington, MA).

CONCLUSIONS

PDT with ALA or MAL is a great option for management of BCCs, especially multiple BCCs and superficial BCCs, and can be combined with debulking procedures, such as curettage, or ablative lasers or penetration enhancers to improve their efficacy. PDT has the advantages of treating the entire field of cancerization, good cosmesis, and noninvasiveness.

Is *Candida* antigen an effective treatment for BCC?

Candida antigen is known to induce a delayed-type hypersensitivity (Type IV) reaction mediated primarily by the TH₁ immune response. Intralesional injections of IL-2 and interferon alpha have previously been shown to cause BCC regression.^{162,163} In addition, lymphocytes infiltrating BCC tumors are known to produce IL-2 and IFN-γ, therefore stimulating the TH₁ immune response.¹⁶⁴ BCCs attempt to combat the TH₁ response by producing IL-10, which is known to inhibit both TH₁ and TH₂ immune responses.¹⁶⁵ In theory, injecting intralesional *Candida* antigen induces a type IV delayed hypersensitivity reaction, ultimately leading to regression of the tumor via cell-mediated immunity.^{166–169}

Intralesional injection of 0.4 mg *Candida* antigen every 6 weeks into nodular or superficial BCC demonstrated that 10 out of the 17 patients had complete histologic clearing of their tumor.¹⁶⁴ Unfortunately, this was only a pilot study, with four people in the control group in whom normal saline was injected intralesionally with no BCC regression at the end of the trial. A Fisher exact test was used and only revealed a p value of 0.105 between experimental and control groups.¹⁶⁴ Perhaps the BCC tumor regression would have been higher in the experimental group if there were more frequent intralesional *Candida* injections, as the delayed-type hypersensitivity reaction lasted only approximately 48–72 hours and was noticeably not active 1 week later when the patient returned for the next injection.¹⁶⁴ Future studies may focus on using an antigen that creates a longer hypersensitivity reaction¹⁶⁴ as well as an antigen that actually causes specific targeting of the tumor, as has been recently accomplished in melanoma,¹⁷⁰ vulvar intraepithelial neoplasia,¹⁷¹ and in murine models of NBCCS.⁹⁷ Out of the 17 subjects assigned to the *Candida* intralesional injection group, 55% experienced pain, 78% experienced pruritus, 21% reported flu-like symptoms, and 12% experienced bleeding.¹⁶⁴

CONCLUSION

Although delayed-type hypersensitivity reaction against the Candida antigen may aid in clearing BCCs, more focused antigenic reactions against certain proteins within a BCC lesion, as has been carried out in other fields, may yield more efficacious results.

Is there an association between statin use and BCC?

Statins are 3-hydroxy-3-methylglutaryl (HMG) coenzyme A reductase inhibitors that target low-density lipoprotein. They are the most commonly prescribed medication in the U.S.¹⁷² Various laboratory studies have demonstrated that statins may play a role in the prevention of BCC. In particular, statins have been shown to act as inhibitors in the sonic hedgehog pathway.^{173,174} *In vitro* and animal model studies have shown statins to inhibit cancer cells' growth.^{175,176} Statins have also been shown to deplete cholesterol and promote apoptosis in keratinocytes.¹⁷⁷ One study demonstrated that statins may increase UV phototoxicity in human cutaneous cell lines, and the effect was shown to be reversible with cholesterol supplementation.¹⁷⁸ Additionally, some statins, such as atorvastatin, are associated with UVB phototoxicity.¹⁷⁹ Another possible mechanism of cutaneous carcinogenesis lies in the theory that statins, specifically simvastatin, may inhibit certain lymphocyte functions, thereby decreasing tumor surveillance.¹⁸⁰ Along those lines, statins have been shown to be carcinogenic in rodents.¹⁸¹ Several noncutaneous neoplasm clinical studies have demonstrated inconsistent results.¹⁸²⁻¹⁸⁵ One recent longitudinal cohort study

examined the relationship between statin therapy and risk for subsequent BCC using data from Kaiser Permanente of Northern California during 1997.¹⁸⁶ Asgari et al. did not find an association between the risk of subsequent BCC and statin use after adjustment. However, before adjusting for age, sex, and health care use, the investigators did observe a higher risk with increasing duration of statin therapy and any use of statin therapy.¹⁸⁶ Remarkably, the study had a 10-year follow-up, and therefore examined the long-term effects of statins on BCC recurrence.¹⁸⁶ The results of this study are consistent with previous large randomized controlled trials that were primarily designed to measure cardiovascular endpoints and that observed a mildly increased risk of nonmelanoma skin cancer that did not quite meet statistical significance.¹⁸⁷⁻¹⁹⁰ One article that reviewed three statin trials did not observe any increased risk for skin cancer; not even a statistically insignificant risk.¹⁹¹ It should be noted that those trials were probably not powered appropriately to detect a relationship between statin use and skin cancer.¹⁸⁶

Further research may be useful to delineate a possible risk of specific statins for BCC. Given that statins are the most commonly prescribed drugs in the U.S., and BCC is the most common cancer, future studies will have a high relevance for public health.¹⁸⁶

CONCLUSION

In vitro studies have demonstrated reasons for and against a possible statin-mediated role in the development of BCCs. After statistical adjustment, Asgari et al. did not observe a statistically significant association between statin use and BCC recurrence.

What We Know

- Basal cell carcinoma (BCC) is the most common malignant neoplasm encountered in humans.
- The average risk for a Caucasian to develop BCC is 30%. In dark-skinned races, the incidence of BCC is 19 times less than in Caucasians.
- Older individuals are affected more than younger individuals.
- Familial and sporadic cases of BCC occur as a result of multiple components of the Sonic Hedge Hog (SHH) pathway becoming dysregulated.
- There are primarily 5 clinical types of BCC: nodular, sclerosing, superficial, pigmented, and cystic.
- There are 5 major histological patterns of BCC: nodular, superficial, micronodular, infiltrative, and morpheaform.
- Surgical excision is the standard of care for BCCs. MMS is the best option for the treatment of aggressive

- BCCs, BCCs on the face, and recurrent BCCs. Nodular BCCs can be managed with SE, radiotherapy, combined ablative lasers with PDT and cryosurgery. PDT is a useful modality for sBCC.
- Metastatic BCC, though a rare condition, should be considered when dealing with aggressive histology, large solitary BCCs, prolonged photodamage, and a positive family history, especially in fair-complexioned population.
- BCCs show a large spectrum of global and local dermoscopic features; heavily pigmented BCCs show the most challenging combinations of dermoscopic features.
- Confocal microscopy has emerged as a very useful modality for diagnosing and monitoring BCCs as well as for expediting Mohs surgery.

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- With close monitoring, cryotherapy is an option used for conventional management of less-aggressive and superficial BCC.
- Lasers have a multifaceted role in BCC treatment. They can be used alone (PDL), as the non-coherent light source for PDT, as ablative therapy for managing the field of cancerization, or as an adjuvant in debulking of the tumor.
- PDT with ALA or MAL is an efficacious option for management of BCCs, especially multiple BCCs and superficial BCCs, and can be combined with debulking procedures, such as curettage, or ablative lasers or penetration enhancers, to improve their efficacy. PDT has the advantages of treating the entire field of cancerization, good cosmesis, and noninvasiveness.

The levels of evidence are as outlined by Sackett and colleagues in *Evidence-Based Medicine: How to Practice and teach EBM*:

1A	Systematic review of randomized controlled trials
1B	Randomized controlled trial with narrow confidence interval
1C	All-or-none case series
2A	Systematic review of cohort studies
2B	Cohort study/low-quality randomized controlled trial
2C	Outcomes research
3A	Systematic review of case-controlled studies
3B	Case-controlled study
4	Case series, poor cohort case-controlled
5	Expert opinion

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Treatment of Cutaneous Squamous Cell Carcinoma

Jennifer D. Bahner, M.D., and Jeremy Bordeaux, M.D., M.P.H.

INTRODUCTION

Nonmelanoma skin cancers (NMSC) are the most common malignancies in the United States, with an annual incidence of over 1 million cases. The vast majority are basal cell carcinoma (BCC) and squamous cell carcinoma (SCC), with a BCC:SCC incidence ratio of 4:1.¹ Unlike almost all BCC, cutaneous SCC is associated with a substantial risk of metastasis, and a small number of patients die from metastatic SCC annually. Risk factors for SCC include childhood sun exposure, ionizing radiation, male gender, light skin, freckling, and treatment with oral psoralen and ultraviolet A (PUVA).²⁻⁵ Incidence of SCC increases with high levels of ultraviolet B exposure⁶ and is highest in lower latitudes, such as Australia and the southern United States. There has been a documented sharp increase in incidence during the past two decades.^{7,8} It is important to identify those lesions (Table 45-1) that have an increased risk (>5%)

of developing metastases to regional lymph nodes. Most cutaneous SCC, however, is low risk and able to be cured with local therapy.

TREATMENT

The aim of treating cutaneous SCC is to completely remove or destroy the tumor while limiting functional and cosmetic impairment. The primary treatment modalities for primary cutaneous SCC are surgical excision, electrodesiccation and curettage (EDC), cryotherapy, Mohs micrographic surgery (MMS), topical agents [i.e., 5-fluorouracil (5-FU), photodynamic therapy (PDT), imiquimod], and radiotherapy (RT). Cryotherapy, EDC, and topical agents are typically reserved for superficial and *in situ* lesions. Excision and MMS are more time-consuming but allow for evaluation of the surgical margins to ensure the lesion has been completely removed.

In selecting the appropriate therapy for SCC, the morbidity of the procedure must be evaluated on a case-by-case basis. The National Comprehensive Cancer Network (www.nccn.org) has published clinical practice guidelines for the treatment of SCC,⁹ although there is a paucity of data from multicenter randomized controlled trials evaluating and comparing treatments for SCC.

SEARCH METHODOLOGY

Reports in the literature were reviewed to identify studies pertaining to treatment of cutaneous squamous cell carcinoma. Articles were retrieved from PubMed by searching for “squamous cell,” “skin” or “cutaneous,” and “cancer” or “carcinoma” concurrently with the name of each therapy. The references from review papers and meta-analyses were also reviewed for relevance. The individual studies were graded using Strength of Recommendation Taxonomy (SORT) criteria¹¹: a Level 1 study contains good quality patient-oriented evidence; a Level 2 study contains limited quality patient-oriented evidence; and Level 3 is other evidence. The strength of each recommendation was then determined based on the body of evidence, again using the SORT criteria: an A strength of recommendation is based on patient-oriented evidence, including consistent findings

TABLE 45-1—Risk Factors for Recurrence, Nodal Metastases of Cutaneous Squamous Cell Carcinoma^{9,10}

History
Recurrent tumor
Rapidly growing tumor
Site of prior radiotherapy or chronic inflammatory process
Neurologic symptoms
Physical examination
Size >2 cm
Location on/around the ear/lower lip
Poorly defined borders
Pathology
Thick and invasive (>4 mm)
Incomplete excision
Moderately or poorly differentiated
Adenoid, adenosquamous, or desmoplastic subtype
Perineural or vascular involvement

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from at least two quality studies; a B recommendation is based on patient-oriented evidence but may not include consistent findings from two quality studies; and a C recommendation is not based on patient-oriented evidence and/or is based on opinion, bench research, consensus guidelines, usual practice, clinical experience, or case series.

RESEARCH QUESTIONS

What are the relative efficacies of common modalities in the treatment of cutaneous SCC (Table 45-2)?

TABLE 45-2—Cutaneous Squamous Cell Carcinoma Recurrence Rates Following Treatment

Modality	Location	Follow-up	Rate of recurrence/metastases
Surgical excision	Lip	5-year 3-year All	45/452 (10%) 23/159 (14.5%) 24/237 (10%)
	All (excluding lip-only papers)	5-year 3-year All	39/285 (13.7%) 9/84 (10.7%) 147/1939 (7.6%)
Electrosurgery	All	5-year <5-year Total	7/357 (2%) 27/896 (3%) 34/1253 (2.7%)
Mohs		5-year <5-year Total	9/308 (2.9%) 51/935 (5.5%) 60/1243 (4.8%)
Radiotherapy	Lip	5-year 3-year All	520/3420 (15.2%) 141/755 (18.7%) 666/4237 (15.7%)
	All (excluding lip-only papers)	5-year 3-year All	24.5/362 (6.8%) 13/228 (5.7%) 30/292 (10.3%)
Cryotherapy	All	All	6/171 (3.5%)

What is the efficacy of surgical excision in the treatment of cutaneous SCC?

Incomplete excision, defined as the presence of cancer cells at the margins of the excision base, is a major risk factor for recurrence. There are data on the recommended surgical margins,¹² risk factors for incomplete excision,¹³ and recurrence of SCC following incomplete excision.¹⁴ The papers in the following table, however, primarily address outcomes following complete excision (i.e., with “clear” or “negative” margins) of primary lesions (Table 45-3).

What is the efficacy of electrosurgery in the treatment of cutaneous SCC?

Although electrosurgery using the combination of electrodesiccation and curettage (EDC) has been used to treat

SCC since the early 20th century, it is currently utilized less frequently than other standard therapies. It is still useful for small, well-defined SCC in low-risk sites. Unlike surgical techniques, it is difficult to standardize and lacks histologic control (Table 45-4).

What is the efficacy of Mohs micrographic surgery in the treatment of cutaneous SCC?

For high-risk NMSC, MMS offers advantages over other treatment modalities, including improved functional and cosmetic outcomes. MMS also allows for the evaluation of 100% of the tissue margins, leading to superior cure rates.⁴⁸ It is, however, time-intensive and requires specialized training (Table 45-5).

What is the efficacy of radiotherapy in the treatment of cutaneous SCC?

Advances in surgical and reconstructive techniques have led to a decline in the use of radiotherapy. RT is still used as adjuvant therapy, particularly for lesions on the head and neck, inoperable lesions, lesions with evidence of perineural invasion, and for patient preference and/or cosmesis (Table 45-6).

CRYOTHERAPY

Cryotherapy destroys malignant cells via freezing and thawing, most commonly using liquid nitrogen. It is fast and cost-effective but does not permit histologic confirmation of the adequacy of treatment margins. In the following studies, multiple techniques were employed, ranging from double liquid nitrogen freeze-thaw technique to using the microthermocouple to freeze to -30°C, thaw to 0°C, and then immediately repeat the cycle (Table 45-7).

OTHER

Topical imiquimod and 5-fluorouracil (5-FU) are both approved by the United States Food and Drug Administration (FDA) for the treatment of actinic keratoses. They are widely used in the treatment of Bowen's disease and SCC in situ, though they are not FDA-approved for these indications and there are limited studies of their efficacy. There are no randomized controlled trials of 5-FU treatment for invasive SCC.⁶⁸ There are a number of case reports or small case series reporting successful use of imiquimod treatment for SCC (Table 45-8), but there is a need for well-designed long-term studies.

Laser and light sources alone and in conjunction with photodynamic therapy (PDT) have been used in the treatment of NMSC; however, the evidence in support of these therapies for invasive cutaneous SCC is limited.⁷⁵ 5-Aminolevulinic acid PDT (ALA-PDT) is highly efficacious in Bowen's disease and actinic keratoses and has demonstrated efficacy in small studies of superficial SCC⁷⁶;

(text continued on page 685)

TABLE 45-3—Efficacy of Surgical Excision for Cutaneous SCC

Paper	Study design	N	Outcome	Follow-up	Level																				
Ashley 1965 ¹⁵	<ul style="list-style-type: none"> Retrospective study Primary SCC Lip Surgical technique & margins varied 	98	<ul style="list-style-type: none"> Recurrence: 9/98 (9.2%) 	5 years	2																				
Brantsch 2008 ¹⁶	<ul style="list-style-type: none"> Prospective study Primary SCC Any location 2-10 mm margins 	615	<ul style="list-style-type: none"> Local recurrence: 20/615 (3%) Metastases: 26/615 (4.2%), of which 6 also had local recurrence 	Mean 43 months (range 1-165)	2																				
Breuninger 1988 ¹⁷	<ul style="list-style-type: none"> No mention of tumor characteristics or invasion Location not reported 2-5 mm margins 	147	<ul style="list-style-type: none"> Local recurrence: 2/147 (1.4%) 	Mean 3 years (range 2-4)	2																				
Creely 1974 ¹⁸	<ul style="list-style-type: none"> Retrospective study Histologically confirmed SCC Originating on mucosa of vermillion border Margin varied from vermilionectomy to resection of most of the lip, depending on tumor size 	91	<table border="1"> <thead> <tr> <th colspan="4">Recurrence</th> </tr> <tr> <th>Size</th> <th>N</th> <th>Local</th> <th>Cervical</th> </tr> </thead> <tbody> <tr> <td>2 cm</td> <td>89</td> <td>15 (17%)</td> <td>4 (4%)</td> </tr> <tr> <td>2-4 cm</td> <td>2</td> <td>2 (100%)</td> <td>1 (50%)</td> </tr> <tr> <td></td> <td></td> <td></td> <td>2 (100%)</td> </tr> </tbody> </table>	Recurrence				Size	N	Local	Cervical	2 cm	89	15 (17%)	4 (4%)	2-4 cm	2	2 (100%)	1 (50%)				2 (100%)	≥ 3 years	2
Recurrence																									
Size	N	Local	Cervical																						
2 cm	89	15 (17%)	4 (4%)																						
2-4 cm	2	2 (100%)	1 (50%)																						
			2 (100%)																						
De Visscher 2002 ¹⁹	<ul style="list-style-type: none"> Prospective study Biopsy-proven primary stage I/II SCC Lower lip 3 mm margins, checked with systematic use of frozen-section analysis 	72	<ul style="list-style-type: none"> Local recurrence: 2/72 (2.8%) at 7 & 17 months post-op <ul style="list-style-type: none"> Among tumors completely excised initially: 1/63 (1.6%) Among tumors incompletely excised initially s/p immediate re-excision: 1/9 (11.1%) Both controlled with surgical re-excision 	Median 5.1 years (range 2-9)	2																				
Dick 1962 ²⁰	<ul style="list-style-type: none"> Histologically proven SCC, 8 of which were previously treated/recurrences; 30 (9%) had enlarged nodes at first visit Lip No note made of the surgical margins used 	41	<ul style="list-style-type: none"> Local recurrence: 1 	3-5 years	2																				
Eberhard 1947 ²¹	<ul style="list-style-type: none"> Biopsy-proven NMSC Any location Cold knife only (no cautery or electric knife used) Margins not reported 	28	<ul style="list-style-type: none"> Crude: actual survival Corrected: uses a correction factor for the probability of not dying within this period Recurrences: 3/28 (10.7%) 	≥3 years	2																				

(Continued)

TABLE 45-3—Efficacy of Surgical Excision for Cutaneous SCC (Continued)

Paper	Study design	N	Outcome	Follow-up	Level																		
Eckert 1944 ²²	<ul style="list-style-type: none"> • Retrospective study • Primary carcinomas (99.3% SCC, 0.7% basosquamous) • Originating at vermillion border of lower lip • Treated by V-excision, margins not reported • Upper lip 	299	<ul style="list-style-type: none"> • Free of local recurrence at 5 years: 281/299 (94%) 	5 years	2																		
Fredricks 1956 ²³	<ul style="list-style-type: none"> • Retrospective study • NMSC treated in plastic surgery center: <ul style="list-style-type: none"> 4 failed previous RT, 1 with +LN External ear Margins varied by lesion location 	12	<ul style="list-style-type: none"> • Free of local recurrence at 5 years: 6/12 (50%) 	≥2 years	2																		
Freeman 1964 ²⁴	<ul style="list-style-type: none"> • Retrospective study • Biopsy-proven NMSC • Any location • Margins not reported 	91	<ul style="list-style-type: none"> Cure rates: <table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>57/59 (96.6%)</td> <td>30/32 (93.8%)</td> </tr> <tr> <td>2</td> <td>48/51 (94.1%)</td> <td>23/27 (85.2%)</td> </tr> <tr> <td>3</td> <td>36/38 (94.7%)</td> <td>18/20 (90%)</td> </tr> <tr> <td>4</td> <td>29/30 (96.7%)</td> <td>13/15 (86.7%)</td> </tr> <tr> <td>5</td> <td>22/23 (95.7%)</td> <td>10/12 (83.3%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	57/59 (96.6%)	30/32 (93.8%)	2	48/51 (94.1%)	23/27 (85.2%)	3	36/38 (94.7%)	18/20 (90%)	4	29/30 (96.7%)	13/15 (86.7%)	5	22/23 (95.7%)	10/12 (83.3%)	1-5 years	2
Years f/u	<2 cm	>2 cm																					
1	57/59 (96.6%)	30/32 (93.8%)																					
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5	22/23 (95.7%)	10/12 (83.3%)																					
Giosci 1967 ²⁵	<ul style="list-style-type: none"> • Histologically confirmed NMSC (4.6% previously treated/recurrent) • 2 had +LN at diagnosis • Any location • 5 mm margins 	31	<ul style="list-style-type: none"> Total recurrences: 2/31 (6.5%) • 1-year recurrence: 0/9 • 2-year recurrence: 1/7 (14.3%) • 3-year recurrence: 1/5 (20%) • 4-year recurrence: 0/6 	1-9 years	2																		
Heller 1979 ²⁶	<ul style="list-style-type: none"> • Retrospective study • Previously untreated non-metastatic SCC • Lip • Through-and-through excision of the lip done in all but the most superficial cases 	169	<ul style="list-style-type: none"> • 5-year survival: 90% • Site of recurrence: 	Duration not specified. Follow-up via direct contact with patient or family	2																		
Hornback 1978 ²⁷	<ul style="list-style-type: none"> • Retrospective study • Biopsy-proven SCC • Lower lip • Margins varied 	27	<ul style="list-style-type: none"> 3-year disease-free survival: <ul style="list-style-type: none"> • Stage I: 25/26 (96.2%) • Stage II: 1/1 (100%) 	3 years	2																		

Immerman 1983 ²⁸	<ul style="list-style-type: none"> Retrospective study Primary invasive SCC Any location Treatment: <ul style="list-style-type: none"> Biopsy + RT: 2 Excision: 84 Positive margins: 24 Subsequent wide excision: 14 Subsequent wide excision + RT: 1 No further treatment: 8 Subsequent recurrence: 2, with successful RT in both 	86	<ul style="list-style-type: none"> Local recurrence: 6/86 (6.9%): <ul style="list-style-type: none"> All remained tumor-free (mean f/u 4.5 years) after retreatment with RT (3), wide excision (2), or re-excision + RT (1). Recurrence involving structures deep to the skin, regional LN, or requiring multiple re-excisions: 11/86 (12.8%): <ul style="list-style-type: none"> Adjuvant RT (7), chemotherapy + RT (2), local hyperthermia + chemo + RT (1) 	Mean 4.3 years (range 1-10)	2									
Jeppsson 1973 ²⁹	<ul style="list-style-type: none"> Histopathologically verified SCC Palpable lymph nodes: 9 (24%) External ear Treatment varied 	38	<ul style="list-style-type: none"> Recurrence by type of surgery: <ul style="list-style-type: none"> Partial resection: 5/26 (19.2%) Total resection: 1/3 (33%) Alive at 5 years: 20 (52.6%) Died of other causes: 15 (39.5%) Died from cancer: 3 (7.9%) 	5 years	2									
Kiviluoto 1964 ³⁰	<ul style="list-style-type: none"> Retrospective study Histologically verified NMSC: <ul style="list-style-type: none"> 751 SCC 99 incipient carcinoma 7 basaloma Neck nodes palpable in 6% of cases Lip Surgical treatment primarily consisted of simple excision 	857	<table border="1"> <thead> <tr> <th>Treatment</th> <th>N</th> <th>5-year net cure rate</th> </tr> </thead> <tbody> <tr> <td>Excision alone</td> <td>22</td> <td>71%</td> </tr> <tr> <td>Excision + RT</td> <td>133</td> <td>84%</td> </tr> </tbody> </table>	Treatment	N	5-year net cure rate	Excision alone	22	71%	Excision + RT	133	84%	5 years	2
Treatment	N	5-year net cure rate												
Excision alone	22	71%												
Excision + RT	133	84%												
Knox 1967 ³¹	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC <ul style="list-style-type: none"> Any location Margins not reported 	211	<table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>160/168 (95.2%)</td> <td>42/43 (97.7%)</td> </tr> <tr> <td>5</td> <td>56/60 (93.3%)</td> <td>21/21 (100%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	160/168 (95.2%)	42/43 (97.7%)	5	56/60 (93.3%)	21/21 (100%)	≥ 1 year (81 with 5-year f/u)	2
Years f/u	<2 cm	>2 cm												
1	160/168 (95.2%)	42/43 (97.7%)												
5	56/60 (93.3%)	21/21 (100%)												
MacKay 1964 ³²	<ul style="list-style-type: none"> Retrospective study Microscopically confirmed SCC <ul style="list-style-type: none"> Lip Margins not reported 	26	<ul style="list-style-type: none"> Apparent control of the primary lesion by initial treatment: <ul style="list-style-type: none"> No LN involvement at time of treatment: 15/21 (71.4%) LN involvement at time of treatment: 3/5 (60%) 	≥ 5 years	2									
MacComber 1959 ³³	<ul style="list-style-type: none"> Retrospective study Primary (83%) & recurrent (17%) NMSC <ul style="list-style-type: none"> Any location Surgical margins not reported 	152	<ul style="list-style-type: none"> 5-year cure rate: 41/44 (93.2%) 	5-year follow-up in 44 patients	2									
Mourouzis 2009 ³⁴	<ul style="list-style-type: none"> Retrospective study Primary SCC (excluding <i>in situ</i>) <ul style="list-style-type: none"> Head/neck (excluding lip) 5 mm margins 	194	<ul style="list-style-type: none"> Incompletely excised: 26 <ul style="list-style-type: none"> Re-excision: 15 Radiotherapy: 11 Regional metastases: 10/194 (5.2%) No note regarding presence or absence of local recurrence 	30-60 months	2									

(Continued)

TABLE 45-3—Efficacy of Surgical Excision for Cutaneous SCC (Continued)

Paper	Study design	N	Outcome	Follow-up	Level
Pless 1976 ³⁵	<ul style="list-style-type: none"> Retrospective study NMSC treated surgically External ear, excluding external meatus 	177	<ul style="list-style-type: none"> 3-year recurrence-free: 85% \pm 3% 5-year recurrence-free: 83.5% \pm 4% Recurrence: 27/177 (15.3%) 5-year survival without recurrence: 56% \pm 4% 	5 years	2
Rank 1958 ³⁶	<ul style="list-style-type: none"> Retrospective study Primary SCC; many referred to surgery center after failure of RT Any location Margins not reported 	57	<ul style="list-style-type: none"> 1-year recurrence rate: 4/55 (7.3%) 3-year recurrence rate: 5/51 (9.8%) 	1-10 years	2
Robinson 1989 ³⁷	<ul style="list-style-type: none"> Retrospective study Primary (69%) & recurrent (31%) cutaneous malignancies treated surgically Any location except penis, vulva, anus Margins not reported 	549	<p>Recurrence rates:</p> <ul style="list-style-type: none"> Recurrence: 9.8-13% Sec. glands: 4.6-6.1% Mets: 1.6-2.2% <p>Range minimum assumes cases lost to f/u were disease-free.</p> <p>Maximum based only on patients with f/u data.</p>	Mean 3.9 years	2
Seretis 2010 ³⁸	<ul style="list-style-type: none"> Retrospective review Excised & histologically proven primary NMSC Head & neck ≥ 5 mm margins 	54	<ul style="list-style-type: none"> Recurrence: 1/54 (1.9%) (all recurrences were 9-26 months after treatment) 	Mean 22 \pm 7 months	2
Shiffman 1975 ³⁹	<ul style="list-style-type: none"> Retrospective study Biopsy-proven primary SCC without invasion or/ mets Pinna Margins not reported 	31	<ul style="list-style-type: none"> Failure of control of disease: 5/31 (16.1%): <ul style="list-style-type: none"> 2 local recurrence 1 LN mets 1 skin mets 1 LN + distant mets 	2 months to >3 years	2
Staub 2008 ⁴⁰	<ul style="list-style-type: none"> Retrospective study Primary NMSC, including 12 SCC followed for >5 years Any location 10 mm margins 	170	<ul style="list-style-type: none"> Recurrence: 4/170 (5%) 	Mean 33 months	2
Werlinger 2002 ⁴¹	<ul style="list-style-type: none"> Retrospective study Primary NMSC Any location 2-4 mm margins 	20	<ul style="list-style-type: none"> No recurrences 	Mean 4.1 years	2
Williamson 1964 ⁴²	<ul style="list-style-type: none"> Retrospective study Biopsy-proven SCC Any location Margins not reported 	23	<ul style="list-style-type: none"> Metastasis: 1/22 (4.5%) 1 patient had metastasis at initial diagnosis 	≤ 5 years	2

NMSC, nonmelanoma skin cancer; SCC, cutaneous squamous cell carcinoma; LN, lymph node(s); Mets, metastasis(es); RT, radiotherapy; 1°, primary; Ipsi, ipsilateral; Contra, contralateral; f/u, follow-up.

TABLE 45-4—Efficacy of Electrosurgery for Cutaneous SCC

Paper	Study design	N	Outcome	Follow-up	Level																		
De Graaf 2006 ⁴³	<ul style="list-style-type: none"> Retrospective study Organ transplant recipients Biopsy-proven, low-risk (<2 cm, ≤3 months) SCC Any location 	211	<ul style="list-style-type: none"> Residual or recurrent SCC: 13/211 (6.2%) in 10/48 patients 85% of these occurred in the 1st 12 weeks after EDC (i.e., were likely residual, not recurrence) 	Mean 50 months (range 3-186)	2																		
Freeman 1964 ²⁴	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC Any location 	407	<ul style="list-style-type: none"> Cure rates: <table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>355/355 (100%)</td> <td>52/52 (100%)</td> </tr> <tr> <td>2</td> <td>302/302 (100%)</td> <td>49/49 (100%)</td> </tr> <tr> <td>3</td> <td>208/209 (99.5%)</td> <td>35/35 (100%)</td> </tr> <tr> <td>4</td> <td>99/101 (98%)</td> <td>17/17 (100%)</td> </tr> <tr> <td>5</td> <td>46/48 (95.8%)</td> <td>9/9 (100%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	355/355 (100%)	52/52 (100%)	2	302/302 (100%)	49/49 (100%)	3	208/209 (99.5%)	35/35 (100%)	4	99/101 (98%)	17/17 (100%)	5	46/48 (95.8%)	9/9 (100%)	1-5 years	2
Years f/u	<2 cm	>2 cm																					
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3	208/209 (99.5%)	35/35 (100%)																					
4	99/101 (98%)	17/17 (100%)																					
5	46/48 (95.8%)	9/9 (100%)																					
Knox 1960 ⁴⁴	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC 2 cycles of EDC Any location 	315	<ul style="list-style-type: none"> 5-year cure rate: 97.06% <ul style="list-style-type: none"> SCC recurrence: 1/34 (2.9%) Treated with only 1 cycle EDC 	6 months - 19 years (≥5-year f/u in 34)	2																		
Knox 1967 ³¹	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC Any location Margins not reported 	545	<ul style="list-style-type: none"> Cure rates: <table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>488/495 (98.6%)</td> <td>50/50 (100%)</td> </tr> <tr> <td>5</td> <td>184/185 (99.5%)</td> <td>28/28 (100%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	488/495 (98.6%)	50/50 (100%)	5	184/185 (99.5%)	28/28 (100%)	≥ 1 year 5-year f/u in 213	2									
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Nemet 2006 ⁴⁵	<ul style="list-style-type: none"> Retrospective study Histologically proven NMSC: at diagnosis, +LN (1), bone spread (1), orbital spread (2) Eyelid 5 mm margins 	68	<ul style="list-style-type: none"> Recurrence: <ul style="list-style-type: none"> Incomplete excision: 1/18 (5.6%) Complete excision: 3/50 (6%) 	Mean 22 months (range 3-125)	2																		
Tromovitch 1965 ⁴⁶	<ul style="list-style-type: none"> Histologically confirmed NMSC Location not specified "Favored" method: 2 cycles EDC with 2-4 mm margin 	29	<ul style="list-style-type: none"> 5-year cure rate: 28/29 (96.6%) 	≥ 5 years (mean 6.8 years)	2																		
Werlinger 2002 ⁴¹	<ul style="list-style-type: none"> Retrospective study Primary NMSC Any location 2-5 mm margins 	56	Recurrence: 2/24 (8.3%)	Mean 4.1 years (>5-year f/u in 24)	2																		

(Continued)

TABLE 45-4—Efficacy of Electrosurgery for Cutaneous SCC (Continued)

Paper	Study design	N	Outcome	Follow-up	Level
Whiting 1978 ⁴⁷	<ul style="list-style-type: none"> Retrospective study All skin tumors treated with EDC in white South Africans Any location 	37 patients, 47 SCC	<ul style="list-style-type: none"> Cure rate: 35/37 (94.5%) 2 recurrences: 1 within 9 months, 1 within 19 months 	Not reported	2
Williamson 1964 ⁴²	<ul style="list-style-type: none"> Retrospective study Biopsy-proven primary SCC Any location 	53	<ul style="list-style-type: none"> Local recurrence: 2/53 (3.8%) <ul style="list-style-type: none"> – 1 basosquamous recurred at 3 months, treated with RT, no mets at 4-year f/u – 1 anaplastic, recurred at 6 months, treated with palliative RT, died 18 months later of carcinomatosis 	≤ 5 years	2

BCC, basal cell carcinoma; EDC, electrodesiccation and curettage; f/u, follow-up; NMSC, nonmelanoma skin cancer; SCC, cutaneous squamous cell carcinoma; RT, radiotherapy.

TABLE 45-5—Efficacy of Mohs Micrographic Surgery for Cutaneous SCC

Paper	Study design	N	Outcome	Follow-up	Level
Dzubow 1982 ⁴⁹	<ul style="list-style-type: none"> • Retrospective study • Primary SCC • Any location 	414	<p>Entire study population:</p> <ul style="list-style-type: none"> • Local recurrence: 14/414 (3.3%) • Metastasis: 3 (0.7%) – none from local recurrence group • 5-year mortality-table adjusted cure rate: 93.3% <p>No previous therapy:</p> <ul style="list-style-type: none"> • Local recurrence: 6/171 (3.5%) • 5-year mortality-table adjusted cure rate: 91.7% <p>Previous unsuccessful therapy:</p> <ul style="list-style-type: none"> • Local recurrence: 8/151 (5.3%) • 5-year mortality-table adjusted cure rate: 90% 	Mean 18.6 months (range 1-136)	2
Leibovitch 2005 ⁵⁰	<ul style="list-style-type: none"> • Prospective multicenter case series • Histologically confirmed primary SCC • Any location (96.3% head/neck) • Standard fresh-frozen MMS technique 	772	<ul style="list-style-type: none"> • 5-year recurrence: 6/229 (2.6%) • No metastatic disease 	229 completed 5-year f/u	2
Leibovitch ⁵¹	<ul style="list-style-type: none"> • Prospective multicenter case series • Cutaneous tumors • Lip • Standard fresh-frozen MMS technique 	96 (73 primary, 23 recurrent)	<ul style="list-style-type: none"> • 5-year recurrence: 0/23 (No note re: primary or recurrent) 	23 completed 5-year f/u	2
Leibovitch 2005 ⁵²	<ul style="list-style-type: none"> • Prospective multicenter case series • SCC with perineural invasion: 36 primary, 34 recurrent • Any location (majority head/neck) • Standard fresh-frozen MMS technique + post-op RT (53%, including both subjects with recurrence) 	70	<ul style="list-style-type: none"> • 5-year recurrence: 2/25 (8%) 	25 completed 5-year f/u	
Leibovitch 2006 ⁵³	<ul style="list-style-type: none"> • Prospective multicenter case series • Primary and recurrent NMSC: 70 primary, 43 recurrent • Scalp • Standard fresh-frozen MMS technique 	113	<ul style="list-style-type: none"> • 5-year recurrence: 1/31 (3.2%) 	31 completed 5-year f/u	2
Robins 1984 ⁵⁴	<ul style="list-style-type: none"> • Retrospective study • Biopsy-proven primary or recurrent NMSC: 23 superficial SCC, 72 ulcerated invasive SCC • Auricle 	96	<ul style="list-style-type: none"> • Recurrence: 23/338 (6.8%) • Outcomes not separated by BCC vs. SCC, primary vs. recurrent 	≥ 1 year	2
Silapunt 2005 ⁵⁵	<ul style="list-style-type: none"> • Chart review and telephone confirmation • Primary invasive SCC treated with MMS • Auricle 	117 pts, 144 SCC	<ul style="list-style-type: none"> • Local recurrence: 5/122 (4.1%) • ≥ 2 years f/u: 5/87 (5.7%) 	Mean 34.6 months (range 7-67)	2
Turner 2000 ⁵⁶	<ul style="list-style-type: none"> • Retrospective study • SCC treated with MMS after debulking (excision or curettage) • Any location 	61	<ul style="list-style-type: none"> • 92% cure rate • Local recurrence: 2/61 (3.3%) • Metastases: 4/61 (6.6%) 	Mean 3.4 years	2

BCC, basal cell carcinoma; EDC, electrode desiccation and curettage; f/u, follow-up; MMS, Mohs micrographic surgery; NMSC, nonmelanoma skin cancer; SCC, cutaneous squamous cell carcinoma.

TABLE 45-6—Efficacy of Radiotherapy for Cutaneous SCC

Paper	Study design	N	Outcome	Follow-up	Level
Ashley 1965 ¹⁵	<ul style="list-style-type: none"> Retrospective study Primary SCC without LN involvement Lip Variied treatment, but most received 3500-6000 rads at 200-300 rad/day 	43	<ul style="list-style-type: none"> 5-year tumor-free: 33/43 (76.7%) Recurrences: 10/43 (23.3%) <ul style="list-style-type: none"> 6/10 had primary lesions ≤ 1 cm 2/10 had primary lesions > 2 cm 5 recurrences in neck 5 recurrences in irradiated area 5-year survival (after RT & resection of recurrence): 91% 	5-year f/u	2
Creely 1974 ¹⁸	<ul style="list-style-type: none"> Retrospective study Histologically confirmed SCC Originating on mucosa of vermillion border of lip 		<ul style="list-style-type: none"> Recurrence Stage: N I: 33 II: 8 Local: Stage I: 7/33 (21%) Stage II: 1/8 (12%) Cervical: 1/33 (3%) 1/8 (12%) 	≥ 3 years	2
Dick 1962 ²⁰	<ul style="list-style-type: none"> Histologically proven SCC 8 previously treated/recurrences, 30 with enlarged LN at diagnosis Lip Most treated with superficial RT, 140 kV, 3850 rads in 7 treatments over 8 days 	287	<ul style="list-style-type: none"> Primary healing: 98% of cases Residual/short-term recurrence: 5/287 (1.7%) Late local recurrence: 4 (though 2 were considered new lesions → 2/287 (0.7%)) 5-year crude percent (n=172): 81.4% 5-year corrected percent: 95% 3-year crude percent (n=287): 90.5% 	3-5 years	2
Eberhard 1947 ²¹	<ul style="list-style-type: none"> Biopsy-proven NMSC Any location X-ray technique varied Interstitial radium 	97	<ul style="list-style-type: none"> Recurrences: 4/97 (4.1%) 	≥3 years	2
Eckert 1944 ²²	<ul style="list-style-type: none"> Retrospective study Primary carcinomas (99.3% SCC, 0.7% basosquamous) Originating at vermillion border of lower lip Treated with radium surface application Upper lip 	121	<ul style="list-style-type: none"> Free of local recurrence at 5 years: 109/121 (90%) Recurrences: 3/72 (4.2%) 	5 years	2
Fischbach 1980 ⁵⁷	<ul style="list-style-type: none"> Primary SCC Any location 	62	<ul style="list-style-type: none"> 5-year recurrence-free survival: 3/6 (50%) Recurrence: <ul style="list-style-type: none"> Primary lesions: 5/62 (8%) <ul style="list-style-type: none"> Stage T₁-T₂: 4/46 (8.7%) One T₁-T₂ patient with local control later died of metastatic lesions 	≥ 2 years	2
Fitzpatrick 1972 ⁵⁸	<ul style="list-style-type: none"> Retrospective study Histologically confirmed NMSC Eyelids (within the orbital margin) 	36 (20 primary)	<ul style="list-style-type: none"> Recurrence: 1/30 (3.3%) 	1-2 years	2

Fitzpatrick 1985 ⁵⁹	<ul style="list-style-type: none"> Retrospective study Histologically proven SCC of the ear or eyelid 	Ear:59 Eyelid:125	Ear:59 Eyelid:125	SCC of ear: - Regional LN mets: 6/59 (10%) - Tumor-related death: 4/59 (7%) SCC of eyelid: not divided by tx (83% XRT, 17% surg., 33% residual/recurrent)	3 years 2																		
Freeman 1964 ²⁴	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC Any location 	88		Cure rates: <table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>68/69 (98.6%)</td> <td>19/19 (100%)</td> </tr> <tr> <td>2</td> <td>66/67 (98.5%)</td> <td>19/19 (100%)</td> </tr> <tr> <td>3</td> <td>59/61 (96.7%)</td> <td>11/14 (78.6%)</td> </tr> <tr> <td>4</td> <td>52/54 (96.3%)</td> <td>10/13 (76.9%)</td> </tr> <tr> <td>5</td> <td>41/44 (93.2%)</td> <td>8/11 (72.7%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	68/69 (98.6%)	19/19 (100%)	2	66/67 (98.5%)	19/19 (100%)	3	59/61 (96.7%)	11/14 (78.6%)	4	52/54 (96.3%)	10/13 (76.9%)	5	41/44 (93.2%)	8/11 (72.7%)	1-5 years 2
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Garcia-Serra 2003 ⁶⁰	<ul style="list-style-type: none"> Retrospective chart review NMSC of head/neck with perineural invasion treated with RT 	Microscopic PNI:48 Clinical PNI:57		<ul style="list-style-type: none"> Local recurrence data not divided into SCC vs. BCC. Microscopic PNI: 9/48 (19%) recurrence to regional LN Clinical PNI: 5/57 (9%) regional recurrence 	Median 4 years (range 2-26) 2																		
Hamalainen 1955 ⁶¹	<ul style="list-style-type: none"> Retrospective study: chart review, f/u exams, questionnaires, annual reports Histologically verified lip carcinomas 	416		3-year recovery rate: 293/416 (70.4%)	≥ 3 years 2																		
Hornback 1978 ²⁷	<ul style="list-style-type: none"> Retrospective study Biopsy-proven SCC Lower lip 250 rads 3 times weekly for 5 weeks 	11		<ul style="list-style-type: none"> 3-year disease-free survival: Stage I: 6/7 (85.7%) Stage II: 4/4 (100%) 	3 years 2																		
Holmes 1982 ⁶²	<ul style="list-style-type: none"> Retrospective study Primary skin tumors Any location, all "difficult treatment sites" Short-distance cobalt unit: 5500 cGy (rad) in 15 daily fractions over 3 weeks 	67		<ul style="list-style-type: none"> Local failure to heal or regress: 8/67 (12%) No recurrences in the follow-up period 	2-8 years 2																		
Kiviluoto 1964 ³⁰	<ul style="list-style-type: none"> Retrospective study Histologically verified NMSC: SCC (751), incipient carcinoma, 7 basaloma) Neck LN palpable in 6% Lip Radiotherapy varied 	857 (751 SCC, 99 incipient carcinoma, 7 basaloma)		<table border="1"> <thead> <tr> <th>Treatment</th> <th>N</th> <th>5 yr net cure rate</th> </tr> </thead> <tbody> <tr> <td>Radium implantation</td> <td>518</td> <td>91%</td> </tr> <tr> <td>X-rays 180 kV</td> <td>75</td> <td>33%</td> </tr> <tr> <td>X-rays 60 kV</td> <td>53</td> <td>90%</td> </tr> <tr> <td>Combined RT</td> <td>56</td> <td>70%</td> </tr> <tr> <td>Excision + RT</td> <td>133</td> <td>84%</td> </tr> </tbody> </table>	Treatment	N	5 yr net cure rate	Radium implantation	518	91%	X-rays 180 kV	75	33%	X-rays 60 kV	53	90%	Combined RT	56	70%	Excision + RT	133	84%	5 years 2
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(Continued)

TABLE 45-6—Efficacy of Radiotherapy for Cutaneous SCC (Continued)

Paper	Study design	N	Outcome	Follow-up	Level																																			
Knox 1967 ³¹	<ul style="list-style-type: none"> Retrospective study Biopsy-proven NMSC Any location Doses not reported 	101	Cure rates: <table border="1"> <thead> <tr> <th>Years f/u</th> <th><2 cm</th> <th>>2 cm</th> </tr> </thead> <tbody> <tr> <td>1</td> <td>74/80 (92.5%)</td> <td>19/21 (90.5%)</td> </tr> <tr> <td>5</td> <td>57/62 (91.9%)</td> <td>12/12 (100%)</td> </tr> </tbody> </table>	Years f/u	<2 cm	>2 cm	1	74/80 (92.5%)	19/21 (90.5%)	5	57/62 (91.9%)	12/12 (100%)	≥ 1 year (5-year f/u in 74)	2																										
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1	74/80 (92.5%)	19/21 (90.5%)																																						
5	57/62 (91.9%)	12/12 (100%)																																						
Lederman 1976 ⁶³	<ul style="list-style-type: none"> Retrospective study Previously untreated NMSC Eyelid or canthus Treatment regimen not detailed 	59	<ul style="list-style-type: none"> 34/51 alive at 5 years (67%) Recurrence-free rates: <ul style="list-style-type: none"> - LN uninvolved: 53/59 (90%) - LN involved <ul style="list-style-type: none"> - initially: 4/59 (6.8%) - later: 2/59 (3.4%) 	5 years (51/59)	2																																			
Mackay 1964 ³²	<ul style="list-style-type: none"> Retrospective study Microscopically confirmed SCC Lip Doses not reported 	2658	<ul style="list-style-type: none"> Apparent control of the primary lesion by initial treatment in cases with ≥5-yr f/u: <ul style="list-style-type: none"> - No LN involv. on adm.: 2060/2415 (85.3%) - LN involv. on adm.: 167/243 (68.7%) 	≥ 5 years	2																																			
Schulte 2005 ⁶⁴	<ul style="list-style-type: none"> Retrospective study Histologically proven NMSC Head and neck Soft x-rays 	245	<table border="1"> <thead> <tr> <th colspan="5">Recurrence rate (%) cumulative after</th> </tr> <tr> <th></th> <th>n</th> <th>5y</th> <th>10y</th> <th>15y</th> </tr> </thead> <tbody> <tr> <td>SCC, total</td> <td>245</td> <td>6</td> <td>10.5</td> <td>12.8</td> </tr> <tr> <td>T1 (≤2cm)</td> <td>79</td> <td>1.7</td> <td>1.7</td> <td>1.7</td> </tr> <tr> <td>T2 (2-5cm)</td> <td>138</td> <td>7.4</td> <td>14.2</td> <td>19</td> </tr> <tr> <td>T3 (>5cm)</td> <td>14</td> <td>25.9</td> <td>25.9</td> <td></td> </tr> <tr> <td>Previously untreated (primary)</td> <td>233</td> <td>5.8</td> <td>9.6</td> <td>12</td> </tr> </tbody> </table>	Recurrence rate (%) cumulative after						n	5y	10y	15y	SCC, total	245	6	10.5	12.8	T1 (≤2cm)	79	1.7	1.7	1.7	T2 (2-5cm)	138	7.4	14.2	19	T3 (>5cm)	14	25.9	25.9		Previously untreated (primary)	233	5.8	9.6	12	Mean 77 months (range 0-181)	2
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Williamson 1964 ⁴²	<ul style="list-style-type: none"> Retrospective study Biopsy-proven SCC 	31	<ul style="list-style-type: none"> Treatment failure: 1/31 (3.2%) Metastases: 2/31 (6.5%) – both present at initial diagnosis/treatment 	≤ 5 years	2																																			

BCC, basal cell carcinoma; EDC, electrodesiccation and curettage; f/u, follow-up; MMS, Mohs micrographic surgery; NMSC, nonmelanoma skin cancer; SCC, cutaneous squamous cell carcinoma.

TABLE 45-7—Efficacy of Cryotherapy for Cutaneous SCC

Study	Design	N	Results	f/u	Level
Holt 1988 ⁶⁵	• Biopsy-proven NMSC • Any location	34	• Recurrence at 6-months post-op: 1/34 (2.9%) • 1 treatment failure (4x5cm scalp tumor)	6 months – 5.5 years	2
Fraunfelder 1980 ⁶⁶	• Biopsy-proven malignancies • Eyelid malignancies	21	• 0/21 recurrences	Mean 21.6 months	2
Wooldridge 1975 ⁶⁷	• Histologically confirmed NMSC • Any location (90% head & neck)	144	• 2-year recurrence: 5/116 (4.3%) • Lip only: 1/27 (3.7%)	2 years	2

NMSC, nonmelanoma skin cancer.

TABLE 45-8—Efficacy of Topical Imiquimod for Cutaneous SCC

Paper	Study design	N	Outcome	Follow-up
Peris 2006 ⁶⁹	• Invasive SCC treated w/imiquimod 5% cream	7	• Complete clearance: 71% • Partial clearance: 29% • No recurrences	Mean 31 months
Tillman 2007 ⁷⁰	• Elderly subjects who were not candidates for surgical excision • Treated with imiquimod for 6 weeks	22	• Biopsy 3 months after therapy: 1 residual tumor • One additional recurrence	Median 26 weeks
Goh 2006 ⁷¹	• Invasive SCC treated with topical imiquimod	2	• Clinical response: 1/2 (50%)	
Oster-Schmidt 2004 ⁷²	• 2 elderly females, multiple comorbidities • Biopsy-proven invasive highly differentiated SCC • Imiquimod 5% cream daily 5 days/week x2 weeks	2	• Case 1: negative biopsy at 3 months, no recurrence 21 months later. • Case 2: negative biopsy at 3 months, no recurrence 8 months later.	8-21 months
Nouri 2003 ⁷³	• Invasive SCC • Imiquimod 5% cream daily for 6 weeks	1	• Negative biopsy at 4 weeks post-treatment	1 month
Martin-Garcia 2005 ⁷⁴	• 43-year-old man with biopsy-proven invasive SCC; refused Mohs • Imiquimod 5% cream daily x 2 weeks then 5 days/week x 10 weeks	1	• Negative biopsy at 2 weeks post-treatment • No recurrence 1 year later	12 months

SCC, squamous cell carcinoma.

however, with recurrence rates up to 69%,⁷⁷ it cannot currently be recommended in the treatment of invasive SCC. In one trial, 225 patients with SCC *in situ* were randomized to receive PDT with methyl aminolevulinate PDT using placebo, cryotherapy, or topical 5-FU.⁷⁸ Twelve months after treatment, the lesion recurrence rates were similar: 15% for MLA-PDT, 21% for cryotherapy, and 17% for 5-FU. Harth et al.⁷⁹ report a modified topical regimen of PDT which achieved complete response in 4/5 (80%) superficial SCC treated. In a randomized intra-patient study, Perrett et al. compared topical 5-FU versus topical MLA-PDT in organ transplant recipients with multiple actinic keratoses and/or carcinoma *in situ*.⁸⁰ In these 8 subjects, PDT proved more effective than 5-FU in achieving complete lesion resolution (complete

resolution rate with PDT: 89%, vs. 5-FU: 11%), as well as superior lesional area reduction, cosmetic outcome, and patient preference.

For advanced cutaneous SCC, there are case reports evaluating the efficacy of various chemotherapy regimens. In one series, four subjects were treated with oral capecitabine and subcutaneous interferon-alpha. Two subjects achieved complete remission, and two achieved partial response; however, the final outcome was complete remission in two, progressive disease, and death from unknown etiology in the fourth.⁸¹ A phase III trial by Brewster et al. demonstrated no decrease in time to recurrence or incidence of second primary tumors following 6 months of adjuvant 13-cis-retinoic acid plus interferon-alfa following surgery and/or radiation for aggressive SCC.⁸² Another

paper reported partial regression of one case of recurrent, locoregionally metastatic SCC following combination therapy with cetuximab, a monoclonal antibody against EGFR, and the COX-2 inhibitor celecoxib.⁸³ Kim et al.⁸⁴ presented a case of a 92-year-old man with history of cutaneous SCC who presented with rapidly growing (>7 cm in 1 month) neck metastasis involving the right carotid artery. This patient was treated with primary cetuximab because of age, comorbidities, and small contralateral lymph node involvement. Seven months after a 3-month regimen of cetuximab, the patient continues to have complete response.

CONCLUSIONS

Although there are many papers reporting the rates of recurrence of cutaneous squamous cell carcinoma following various therapies, there is a paucity of randomized-controlled trials comparing therapies. The methodology and follow-up are also not standardized, making it difficult to compare data between case series. Large-scale well-designed studies with long-term follow-up are needed to reach reliable and meaningful conclusions. Based on the data available (see Table 45-2), there appear to be higher rates of recurrence following surgical excision and radiation than following electrosurgery, Mohs micrographic surgery, and cryotherapy. This may, however, simply be a product of the patient population selected for each treatment type.

The National Comprehensive Cancer Network (NCCN) publishes guidelines for care of nonmelanoma skin cancers.⁸⁵ Although these guidelines are based on author consensus and are a work in progress, they are currently the best algorithm for making treatment decisions for cutaneous SCC. They include guidelines for local lesions as well as those with either palpable regional lymph nodes or palpable intraparotid mass. Local lesions are then considered to be at either high or low risk of recurrence based on such clinical factors as location, size, and rapidity of growth, as well as such pathologic characteristics as degree of differentiation and Clark level or thickness. Based on these and other factors, such as age of patient and location of lesion, the guidelines give recommendations for treatment.

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Treatment of Cutaneous Melanoma

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METHODS

PubMed's MEDLINE database and the Melanoma Molecular Map Project's interactive multidatabase¹ were searched for full-text articles using the following key words: "Melanoma," "Melanoma treatment," "Surgical treatment of melanoma," and "Melanoma lymph node evaluation." The most relevant randomized controlled trials with best supporting evidence for current treatment guidelines were selected from the search results to be used as references in this chapter.

SURGICAL TREATMENT OF MELANOMA

Once the diagnosis of melanoma has been established, the tumor is carefully examined to determine how deeply it has penetrated into the skin. This degree of skin invasion is known as the "tumor microstage." The microstage has significant bearing upon type of treatment, prognosis, and survival, and is most often described in terms of Clark's level and Breslow thickness.

The definitive surgical treatment for primary cutaneous melanoma is a wide local excision (WLE) down to the deep fascia. The recommended surgical margins are based on the depth of the tumor (Breslow measurement). Multiple large clinical trials have examined the impact of the surgical margin on the local recurrence rate (Table 46-1).

Melanoma In Situ

For patients with in situ melanomas, there are no data from randomized trials to define the optimal extent of surgical resection. However, retrospective data support the routine use of 0.5 cm margins.^{11,12}

Invasive Melanomas

For melanomas up to 1 mm in depth, a surgical margin of 1 cm is recommended.¹¹ For melanomas 1-4 mm in depth, randomized prospective studies show that 2-cm margins are appropriate, although 1-cm margins have been proven effective for tumors of 1- to 2-mm thickness.^{3,9} A well-conducted retrospective study of high-risk primary

melanomas (>4 mm thickness, median depth 6 mm) showed that excisional margins greater than 2 cm have no effect on local recurrence, disease-free survival (DFS), or overall survival (OS) rates; therefore, a 2-cm margin is likely appropriate in this subgroup.¹³

SENTINEL LYMPH NODE BIOPSY

Sentinel lymph node biopsy (SLNB) has replaced elective regional nodal dissection for the evaluation of regional nodal status. Sentinel lymph node (SLN) status (positive or negative) is the most important prognostic factor for recurrence and is the most powerful predictor of survival in melanoma patients. In a study of 612 patients with cutaneous melanoma (stage I/II), negative results from SLNB were associated with a nearly 60% increase in 3-year disease-free survival compared with positive SLNB results.¹⁴

In the fall of 2006, the results of the third of five planned interim analyses of the Multicenter Selective Lymphadenectomy Trial-1 (MSLT-1) were published.¹⁵ This trial was performed to compare the outcomes of patients with newly diagnosed cutaneous melanoma treated with either WLE plus observation of the regional nodes, followed by regional lymphadenectomy if nodal metastases became clinically apparent (the observation group), or WLE plus SLNB (the SLN group) and: (1) immediate regional lymphadenectomy if a SLN was positive (i.e., selective lymphadenectomy), or (2) observation if the SLN was negative. The primary goal was to assess the survival impact of SLNB. The trial also addressed several other questions regarding the use of SLNB in the initial management of patients with melanoma.

This interim analysis of the MSLT-1 confirms previous reports that SLN status is the most powerful independent predictor of survival, but it does not provide a definitive answer on whether SLN biopsy provides a survival advantage. With a median follow-up of 5 years, this analysis showed a 3%, nonsignificant survival advantage for patients in the SLN group.

A secondary analysis from the MSLT-1 trial compared the patients who had positive SLNs and underwent immediate lymphadenectomy versus the patients in the

TABLE 46-1—Trials Investigating Surgical Margin Width for Melanoma Resection

Study	N	Median follow-up	Melanoma thickness	Margins	Local recurrence (%)	Overall survival (%)
World Health Organization ^{2–4}	612	12 yrs	0–1 mm 1.1–2 mm 0–1 mm 1.1–2 mm	1 cm 1 cm 3 cm 3 cm	3/186 (1.6) 5/119 (4.2) 1/173 (0.6) 2/134 (1.5)	87 85
Swedish ⁵ Cohn-Cedarmark G, 2000	989	11 yrs	0.8–2 mm	2 cm 5 cm	3/476 (0.6) 5/513 (1)	79 76
French Cooperative Group ⁶ Khayat D, 2003	326	16 yrs	<2.1 mm	2 cm 5 cm	1/181 (0.55) 4/185 (2.1)	87 86
Melanoma Intergroup Trial ^{7–9} Karakoussis CP, 1996	468	8 yrs	1–4 mm	2 cm 4 cm	(2.1) (2.6)	80 84
British Trial ¹⁰ Thomas JM, 2004	900	60 mos	2 mm	1 cm 3 cm	15/453 (3.3) 13/457 (2.8)	No significant difference

observation group who later developed palpable nodal disease. The results from this analysis are particularly important to note: there was a significant progression to more advanced nodal disease in the nodal observation group, and there was a significant survival advantage (20%) for the SLN-positive patients who underwent immediate lymphadenectomy.¹⁶ However, this remains highly controversial, as discussed by Sondak et al.¹⁷

In general, SLN biopsy is indicated for melanomas >1.0 mm and for tumors 1 mm or less when histologic ulceration is present and/or classified as Clark level 4 or higher. Patients with clinically enlarged lymph nodes and no evidence of distant disease should undergo a complete regional lymph node dissection.

Standard of care is to perform a complete lymph node dissection (CLND) in melanoma patients with positive SLNs. However, less than 20% will have metastases in non-SLNs. The S classification was described in an attempt to predict the non-SLN status, hoping to identify a subset of patients who can be spared the CLND. This classification is based on the progression of melanoma metastasis from the outside of the lymph node through afferent vessels to the subcapsular lymphatic sinuses through intracapsular lymphatic channels.¹⁸ From there, they reach in a centripetal fashion the deeper part of the node. The occurrence of non-SLN metastasis is significantly related to this S classification ($P = 0.010$), and it has a high prognostic correlation.¹⁹ Studies aimed at assessing the feasibility and usefulness of this method suggest that the S classification predicts the status of non-SLNs.^{20,21} No patient with status was found to have additional non-SLN positive nodes.²¹ Thus larger-scale trials are necessary to confirm these results, as they offer the potential for sparing patients the morbidity of CLND with a positive SLN.

FOLLOW-UP FOR PRIMARY MELANOMA

Patients should be monitored regularly after a diagnosis of cutaneous melanoma, particularly in the setting of

TABLE 46-2—Follow-Up Guidelines²¹

Stage	History and physical examination	Chest radiograph (CXR)/laboratory studies*
Stage IA	6 months × 2 years 12 months thereafter	No
Stage I/II Breslow depth = 1.0–4.0 mm	4–6 months × 3 years 12 months thereafter	Initial: CXR, optional CBC, LFT Follow-up: Yearly CXR, optional CBC, LDH
Stage I/II Breslow depth >4.0 mm	4–6 months × 3 years 12 months thereafter	Initial: CXR, optional CBC, LFT Follow-up: Yearly CXR, optional CBC, LDH
Stage III/IV	3–4 months × 5 years 12 months thereafter	Initial: CXR and CT scans Initial: CBC, LFTs, LDH (for staging) Follow-up: q 6–12 mo CXR, LFT

*LFT are LDH, AST, ALT, and Alk Phos. LDH is lactate dehydrogenase.

thicker tumors, because most metastases occur in the first 1–3 years after treatment of the primary tumor. Annual skin examinations are recommended for life because an estimated 4–8% of patients with a history of melanoma develop new primary melanoma, generally within the first 3–5 years following diagnosis (Table 46-2).²²

RADIATION THERAPY FOR CUTANEOUS MELANOMA

Melanoma cell lines possess a marked ability to repair damaged intracellular contents and recover from radiation-induced damage compared to other cell lines.^{23–26} While melanoma is generally considered a radio-resistant tumor, radiation therapy has proved to be effective treatment for lentigo maligna melanoma (LMM) and lentigo maligna. These melanomas are slow growing, have low metastatic

potential, and were confined to either the epidermis or dermis; attributes which make them responsive to RT alone.^{27,28} In a series of 95 cases in which high radiation doses of 100-110 Gy were delivered in 6 Gy fractions, a 68% 5-year survival rate was obtained, similar to that obtained with local-wide excision.²⁹ However, RT has often been employed nihilistically in patients with a relatively low probability of achieving long-term control because of presentations of large, unresectable, or incompletely resectable locoregional disease.^{30,31} To this end, it has often been administered in palliative settings, in cases of localized (usually unresectable) metastatic disease.^{32,33} In 2006, a prospective Phase II study by the Trans-Tasman Radiation Oncology Group (TROG) treated two hundred and thirty-four patients with melanoma involving lymph nodes with 48 Gy in 20 fractions to the high-risk nodal regions. In contrast to the suggestion that melanoma is unresponsive to RT, regional in-field relapses occurred in only 16/234 patients (6.8%). The progression-free survival and regional control rates were 27% and 91%, respectively, at 5 years, with the major problem being distant metastasis.^{34,35} A randomized Phase III study is underway to confirm the efficacy of local-regional radiation for patients with head and neck melanoma.³⁶

ADJUVANT TREATMENT OF REGIONAL MELANOMA

High-dose interferon α 2b (IFN) is approved as postsurgical adjuvant immunotherapy in patients with resected stage IIB-III melanoma. Based primarily on three Eastern Cooperative Oncology Group (ECOG) trials (E1684, E1690 & E1694), which showed a statistically significant improvement in RFS and OS. Wheatly et al. reported a meta-analysis of 13 randomized trials that demonstrated significant benefit of IFN for OS odds ratio 0.9 ($p=.008$), although the impact on survival appears to be small. The European Organization for Research and Treatment of Cancers (EORTC) has evaluated PEG-IFN α 2b for 5 years versus observation (EORTC 18991). The primary endpoint was distant metastasis-free survival, and at 3.8 years median follow-up there was a nonsignificant benefit in favor of PEG-IFN α 2b. In summary, IFN seems to provide benefit in terms of RFS, but its impact on OS is modest and further studies are underway to identify subsets most likely to derive benefit.

MELANOMA-SPECIFIC VACCINES

Numerous approaches to the development of melanoma-specific vaccines have been disappointing. A vaccine prepared from three allogeneic melanoma cell lines using BCG as an adjuvant (Canvaxin) was studied in two phase III trials in patients with resected stage III and resected stage IV melanoma. In 2005, the Data Safety Monitoring Board overseeing these two studies determined that the trials were sufficiently unlikely to result in a determination

of vaccine efficacy, and each trial was ended and all protocol treatments were discontinued. The Southwest Oncology Group conducted a randomized phase III trial of an allogeneic melanoma vaccine (Melaccine) versus observation in patients with intermediate-thickness, clinically or pathologically node-negative melanoma. Six hundred eighty-nine patients were accrued. After a median follow-up of 5.6 years, the vaccine was not associated with a statistically significant benefit in disease-free or overall survival.³⁷

Melanoma-defined antigen vaccines include targets such as gangliosides and antigens recognized by T cells infiltrating melanoma lesions. Gangliosides are attractive targets for immunotherapy because of their ability to induce antibody responses. GM2 administered with BCG or in combination with the keyhole limpet hemocyanin (KLH) hapten are effective modes of inducing GM2-specific antibodies.³⁸⁻⁴⁰ Despite this, two large phase III trials have demonstrated no evidence of a survival benefit when a vaccine using GM2-KLH was used and also suggested that vaccination may have a negative effect on survival. Numerous T cell antigens identified in patients with melanoma also are the basis for ongoing efforts in vaccine development. Specifically, MAGE-3 protein, which contains both HLA-A1 and HLA-2.1 restricted CTL epitopes, is able to induce both a specific antibody response and a cellular immune response in patients with advanced melanoma.⁴¹ Gene expression profiling studies can demonstrate specific markers that are associated with improved clinical response to the MAGE-3 vaccine, such as the MAGE-A3 gene signature.^{42,43} Currently, an international phase III trial is underway to evaluate the MAGE-A3 vaccine in patients with completely resected stage III melanoma and the MAGE-A3 expression profile in their resected lymph node (NCT00796445).

SYSTEMIC TREATMENT OF ADVANCED MELANOMA

Interleukin-2 is an approved treatment in metastatic melanoma, because a small number of patients can achieve a durable complete response and may in fact be “cured.” The toxicity is manageable and IL-2 is a reasonable option for some patients, although there are no phase III data.

Chemotherapy is ineffective in metastatic melanoma. Dacarbazine is often the standard-of-care arm in phase III trials but it has no impact on survival and the time to progression is generally 6-8 weeks. It may be useful for palliation in some patients.

Korn et al. reported a meta-analysis of phase II trials performed in the cooperative group setting from 1975 to 2005. Seventy trial arms were analyzed and parameters are defined to evaluate and plan future phase III trials.

BIOCHEMOTHERAPY

In an effort to enhance response rates, chemotherapy agents are often combined with other chemotherapeutic

or biologic agents. Regimens consisting of combinations of IL-2 or IFN- α , or both, administered with chemotherapy produced high response rates in the treatment of MM in phase 2 trials. Unfortunately, all failed to demonstrate a statistically significant benefit in overall survival compared to chemotherapy regimens.^{44–49}

The combination of cisplatin, vinblastine, and dacarbazine (CVD) with IL-2 and IFN- α is an extensively used biochemotherapy regimen that yields the highest overall response rate.^{44,45,47,50,51} A large phase III trial compared CVD with CVD plus IFN- α and IL-2 administered concurrently and demonstrated no significant difference between the biochemotherapy and chemotherapy arms in response rates and survival.⁵²

Despite the apparent high response rates from biochemotherapy, no overall survival advantage is conveyed when compared to chemotherapy alone.

ANTI-CTLA-4 MONOCLONAL ANTIBODIES

T cells recognize intracellular protein peptide fragments displayed on the surface of antigen presenting cells (APCs). This recognition is a critical event in the activation of cellular immunity. The interaction of T cells with APCs requires the presence of the co-stimulatory molecule B7. Subsequent activation results in upregulation of cytotoxic T-lymphocyte antigen 4 (CTLA-4). CTLA-4 then competes for binding with B7 and negatively inhibits T cell activation. Therefore, monoclonal antibodies (MAbs) targeting CTLA-4 have the potential to promote immune responses in melanoma patients, where such responses are associated with disease regression.

Ipilimumab and tremelimumab are two CTLA-4 MAbs currently being evaluated in melanoma patients. Several studies demonstrate significant and lasting responses to ipilimumab in a subset of patients with unresectable or metastatic melanoma. A delayed response of weeks to months is sometimes observed.⁵³ There is also an associated potential for autoimmune toxicity, including enterocolitis and hypophysitis.⁵⁴ In a phase II trial of 72 chemotherapy-naïve patients with advanced melanoma randomly assigned to ipilimumab with or without dacarbazine, the disease control rate was increased with the combined treatment (31 versus 22 percent with ipilimumab alone).⁵⁵ Tremilimumab showed similar activity in phase I and II clinical studies in previously treated patients.⁵⁶ Preliminary results of a phase III clinical trial comparing tremilimumab to chemotherapy (either temozolamide or dacarbazine) in 655 previously untreated patients with metastatic melanoma⁵⁷ showed no statistical difference in the objective response rate for overall survival (American Society of Clinical Oncology meeting, 2008). Longer follow-up is required to determine if tremilimumab yields more lasting responses than cytotoxic chemotherapy.

A recently published phase III study of ipilimumab randomized 676 patients with unresectable stage III or IV melanoma, whose disease had progressed while receiving therapy for metastatic disease, in a 3:1:1 ratio to receive ipilimumab plus gp100 (a peptide vaccine), ipilimumab alone, or gp100 alone, administered every 3 weeks for up to four treatments.⁵⁸ The median overall survival was statistically higher among patients receiving ipilimumab plus gp100 compared to patients receiving gp100 alone (10.0 months vs 6.4 months), whereas there was no difference in overall survival between the ipilimumab groups with or without gp100. These data suggest that ipilimumab, with or without gp100, improves overall survival in patients previously treated with metastatic melanoma. Until now, no randomized studies had ever shown a clear survival benefit with any agent or combination of agents.

MOLECULARLY TARGETED THERAPY

Recent advances in the molecular biology of melanoma tumorigenesis have enhanced our understanding of features critical for effective melanoma cell death and resistance mechanisms. Gain-of-function KIT mutations were reported in 21% of mucosal melanomas, 11% of acral melanomas, and 16.7% of melanomas arising in chronically sun-damaged skin,⁵⁹ while 15% of anal melanomas harbored a KIT oncogenic mutation⁶⁰ and in other cases showed increased KIT copy number or amplification. Most mutations affect the juxtamembrane region of the KIT protein, which predicts responsiveness to imatinib mesylate.⁶¹ In *in vitro* assays, mucosal melanoma cells exhibited imatinib sensitivity, which correlated with KIT mutational status.⁶² In these studies, imatinib dramatically decreased proliferation and was cytotoxic to a KIT mutated and amplified cell culture, suggesting that these mutations may serve as mediators and/or biomarkers of *in vivo* treatment efficacy. Preliminary findings from trials of imatinib or other c-KIT inhibitors in melanoma patients demonstrate a 50% response rate with imatinib in metastatic melanoma patients with a c-KIT mutation in their tumor.⁶³ Investigators are actively working to identify the optimal inhibitors to use for the most common c-KIT mutations found in melanoma.^{64,65}

The RAS-RAF-MAPK signaling pathway is an important signaling pathway that mediates a number of cellular responses to growth signals. Activating mutations of RAS and BRAF result in a constant activation of the MAP kinase cascade and eventually contribute to proliferation and dedifferentiation of cancer cells. Activating mutations of BRAF have been observed in approximately 50% of malignant melanomas. The V600E mutant accounting for over 90% of these mutations leads to a continuous stimulation of the MAP kinase pathway, resulting in uncontrolled cancer cell growth.^{66,67} While numerous amino acids within

the BRAF protein are targets for mutation in melanoma,⁶⁷ valine at position 600 (BRAF^{V600E}) is the most predominately targeted residue, comprising 95% of all BRAF mutations in melanoma.^{67–69} Not only is this mutation present in primary tumors and metastases, but it is also found in benign nevi,^{70,71} suggesting that while activating BRAF mutations portend a growth advantage to melanocytic cells, these mutations are not sufficient to fully transform normal human melanocytes. Various small-molecule inhibitors with improved RAF kinase selectivity, such as Raf265 (Novartis), XL281 (Exelixis/Bristol Myers Squibb), AZ628 (AstraZeneca), SB-59088 (GlaxoSmithKline) and PLX-4032 (Plexxikon/Roche), hold promise for evaluating BRAF mutations as therapeutic targets in clinical studies.

PLX-4032 is highly selective for BRAF, exhibits tenfold greater potency for BRAF^{V600E} over wild-type BRAF, has excellent oral bioavailability, and has a relatively low toxicity profile.⁷² This agent is currently under investigation as a form of treatment in advanced melanoma (www.clinicaltrials.gov), and results of a phase I trial have been reported recently.⁷³ In the beginning stage of the phase I trial, cohorts of patients with advanced solid tumors were treated with increasing doses of PLX4032 (200 to 1,600 micrograms), administered twice daily as oral capsules. During the dose-escalation stage of the phase I trial, 21 patients with metastatic melanoma, 16 with, and 5 without, BRAF mutations, were treated at doses that achieved AUC_{0–24} >300 μMh. Tumor dimensions were measured by computed tomography (CT). Ten patients with BRAF-mutant melanoma achieved a partial response with tumor regression and one patient had a complete response; none of the patients with melanomas who were wild-type for BRAF achieved tumor regression. In a follow-up study of 32 participants, tumor size decreased in 24 and disappeared entirely in two

patients with BRAF mutations. There is the potential for patients with metastatic melanoma to undergo screening before the initiation of therapy for the presence of mutations in BRAF, KIT, and probably other key genes.

Melanoma, like many other cancers, displays epigenetic abnormalities, such as global losses and local gains in methylation patterns, which likely portend a tumor survival advantage through silencing of tumor suppressor genes.^{74–77} With advanced molecular biologic techniques, researchers can use methylated DNA immunoprecipitation and promoter array hybridization to determine relative methylation in normal human melanocyte and melanoma cells, allowing for identification of unique tumor-specific methylation markers.⁷⁸ CpG methylation represents a reversible event, thus silenced tumor suppressor genes represent potential anticancer therapy targets. Decitabine is a cytosine analog that induces genome hypomethylation and is an agent with potential to upregulate silenced genes.⁷⁹ Recent studies aimed at classifying gene upregulation based on promoter methylation and CpG content underscore that understanding patterns of decitabine action could facilitate predicting the likelihood of upregulating silenced tumor suppressor genes.⁸⁰

RNA interference (RNAi) is a technique for turning off specific genes, but until recently, its translation into clinical cancer therapy has been a struggle, given the challenge of delivering the short sequences of interfering RNA to cellular targets.^{81,82} Recent phase I clinical trials, however, demonstrate RNAi-mediated reduction of ribonucleotide reductase subunit M2 expression from melanoma biopsies of patients who received intravenous infusions with small interfering RNAs (siRNA).⁸³ Therefore, anticancer therapies that target RNAs seem to be one step closer to a new class of targeted melanoma therapy.

What We Know: Therapeutic Management of Melanoma

- The definitive surgical treatment for primary cutaneous melanoma is a wide local excision (WLE) down to the deep fascia.
- Sentinel node status (positive or negative) is the most important prognostic factor for recurrence and is the most powerful predictor of survival in melanoma patients.
- Standard of care is to perform a complete lymph node dissection (CLND) in melanoma patients with positive SLNs.
- Annual skin examinations are recommended for life because an estimated 4-8% of patients with a history of melanoma develop new primary melanoma, generally within the first 3-5 years following diagnosis.
- Melanoma is generally a radio-resistant tumor, and radiation therapy is reserved for specific cases of lentigo maligna and lentigo maligna melanoma (LMM), and in the palliative setting.
- Ipilimumab (MAb targeting CTLA-4) has the potential to promote immune responses in melanoma patients, where such responses are associated with disease regression. Ipilimumab has demonstrated a survival advantage in a randomized-controlled trial.
- Melanoma cells frequently display gain-of-function c-KIT mutations, activating BRAF, and epigenetic abnormalities, such as global losses and local gains in methylation patterns, all of which likely translate into tumor cell growth and survival advantages. These are important and promising areas of ongoing research.

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Treatment of Mycosis Fungoides and Sézary Syndrome

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INTRODUCTION

Cutaneous T cell lymphomas (CTCL) are T cell non-Hodgkin lymphomas (NHL) with primary cutaneous involvement. Mycosis fungoides (MF) and Sézary syndrome (SS) are subsets of CTCL.¹ The diagnosis and work-up for MF and SS are outlined in the National Comprehensive Cancer Network (NCCN) practice guidelines.²

Mycosis fungoides is the most common type of CTCL with a unique clinical-pathologic presentation. The initial cutaneous presentation of MF can be as patches or plaques that may subsequently evolve into tumors or generalized erythroderma.³ Patches or plaques in MF are often localized, typically affecting flexural areas and the buttocks, although any area of the body can be involved. However, the skin involvement can be much more extensive and sometimes may progress to tumors or generalized erythroderma involving the entire skin surface. In the more generalized presentations, keratoderma may develop, nails may become dystrophic, and scalp involvement can result in alopecia.¹

Sézary syndrome (SS) is a distinct subtype of CTCL, which is characterized by erythroderma, lymphadenopathy, and neoplastic T cells (or Sézary cells) in the peripheral blood that meet criteria of significance either by morphology, flow cytometry, or molecular analysis.^{4,5} Patients may present initially with all components of SS or with only one component (e.g., generalized erythroderma), and subsequently progress to develop other clinical features of SS.

Accurate staging is important because therapeutic approaches in MF are largely based on the clinical stage of the disease. The standard clinical staging system for MF and SS is based on the extent and type of skin involvement (T classification), the presence of lymph node (N classification) or visceral disease (M classification), and the detection of abnormal (Sézary) cells in the peripheral blood (B classification).⁴

The risk of extracutaneous disease tends to correlate with the extent and type of skin involvement.^{6,7} The extent and type of skin involvement are defined in the T-classification in the revised staging system.⁴ T1 disease is defined as less than 10% of the skin surface involved with patches or plaques while T2 disease is defined as greater than 10% but less than 80% of the skin surface involved with patches or plaques. T3 disease is defined as

tumor (nodular) disease, and T4 disease is erythroderma with at least 80% of the skin surface diffusely involved. Extracutaneous involvement at presentation is exceedingly rare in patients with T1 disease, infrequent in patients with T2 disease (2%), and (more) likely in patients with T3 (13%) or T4 (24%) disease.^{7,8} Patients who present with limited cutaneous involvement (T1) may never progress to more advanced T classification, especially when appropriate treatment is administered.^{6,9,10} Although MF may be a systemic disease from the outset, the clinical behavior is such that progression of skin disease precedes onset of clinical symptoms at extracutaneous sites. Any visceral site can be involved with MF, the most common of which are the lungs, bone marrow, gastrointestinal tract, liver, and central nervous system.¹¹

EPIDEMIOLOGY AND ETIOLOGY

Although MF and SS are uncommon forms of NHL, they are the most common lymphomas with primary involvement of the skin. The annual incidence in the United States is estimated at 0.96 cases per 100,000 with approximately 3,000 new cases per year in the United States.¹² While MF and SS occur in children and young adults, the median age at diagnosis is between 55 and 60 years.¹³ There is 2:1 male predominance, and black patients have a two-fold greater risk for developing MF/SS than white.

The etiology of MF and SS remains undetermined. Various studies and case reports have suggested an association with genetic factors, environmental exposure, or an infectious etiology, but none has confirmed a causal association. The immunopathogenesis has been a focus of much research in the last decade. The malignant lymphocytes in mycosis fungoides are CD4⁺T cells that express the skin-homing receptors CLA and CCR4. The malignant cells are associated with increased T helper type 2 and reduced T helper type 1 cytokine production.³ The trigger of T cell activation and subsequent clonal expansion of the malignant T cells in the skin remains unclear.

METHODOLOGY

While there are multiple therapeutic options for MF and SS, there is a lack of well-designed, prospective, controlled

clinical trials comparing the efficacy and safety of various therapies. There are also no standardized response criteria. Many studies use skin response as the primary endpoint only while others used composite or global responses as the primary endpoint. As a result, caution is needed when interpreting efficacy data such as duration of response and time to response. The most important factor in designing a treatment plan is the clinical stage. Selection of a specific treatment plan is based on the clinical stage, additional prognostic factors (e.g., folliculotropism or large cell transformation), toxicities associated with the treatment options, the patient's age, and other social and medical problems (Figures 47-1 thru 47-5). The NCCN as well as the European Organisation for the Research and Treatment of Cancer (EORTC) outline the treatment guidelines for MF and SS according to stage of disease.^{2,14} In considering all possible therapeutic options for a given stage of disease, retrospective cohort as well prospective studies were reviewed. Subsequently, the studies were evaluated using the U.S. Preventive Services Task Force: Hierarchy of Evidence (Table 47-1).¹⁵

In general, the treatment options in MF/SS are categorized into skin-directed treatments, systemic biologic/noncytotoxic therapies, and systemic cytotoxic chemotherapies. For patients with T1 and T2 disease without extracutaneous involvement, stages IA-IIA, the primary treatment plan will usually be limited to skin-directed therapies (Tables 47-2 thru 47-5). However, if these fail or there is histologic evidence of either large cell transformation or folliculotropism, a more intensive regimen is usually indicated (Tables 47-6 thru 47-7). With respect to tumor

disease, stage IIB, the treatment plan depends on the extent of the tumor lesions. If the tumor lesions are few in number, the skin directed treatment options for stage IA-IIA are indicated, and the tumor lesions should be treated with local radiation (Table 47-8). In cases with extensive tumor involvement, total skin electron beam therapy or systemic therapies are considered (Tables 47-9 and 47-10). The affected skin in patients with erythroderma (T4) is very sensitive and cannot tolerate skin-directed treatment. Hence, primary therapy for patients with erythroderma consists of the use of systemic biologic response modifiers (e.g., photopheresis, and oral retinoids/rexinoids, interferons), histone deacetylase inhibitors (HDAC-i), denileukin diftitox (fusion toxin), or low-dose methotrexate monotherapy or in combination (Tables 47-11 thru 47-15). When biologic therapies fail in patients with refractory stage IIB to IV disease, single-agent chemotherapy such as gemcitabine, or liposomal doxorubicin are considered (Table 47-9).

Effective supportive care is critical in the management of patients with T4 disease. Increased susceptibility to bacterial and viral infection is a considerable source of morbidity and mortality. Patients with this type of compromise to the skin barrier should have diligent surveillance for skin infections, especially *Staphylococcus aureus* and herpes simplex virus. There is a low threshold for beginning systemic and skin-directed antibacterial agents with the appropriate susceptibilities.

Mycosis fungoides and Sézary syndrome are associated with severe pruritus, which can be a serious detriment to patient quality of life. The measurement of this very subjective symptom is important to assess improvements in

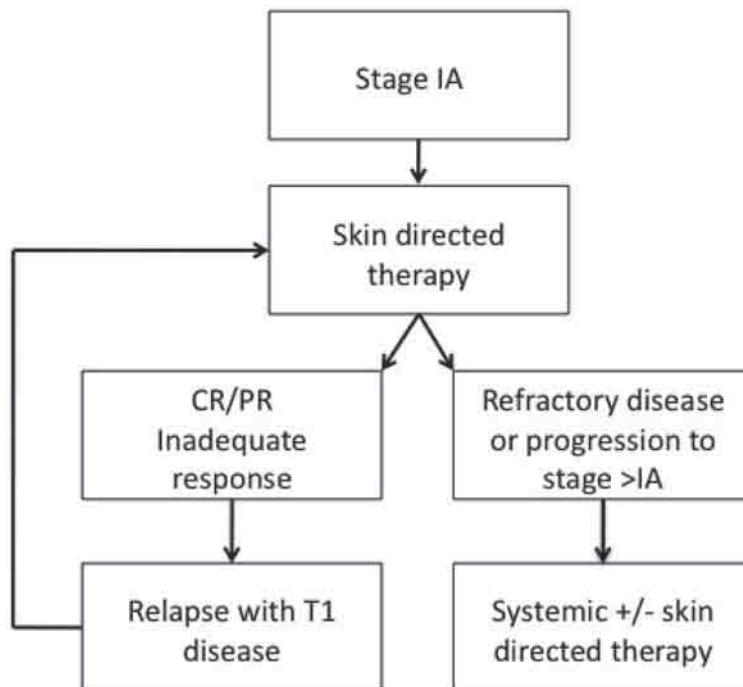
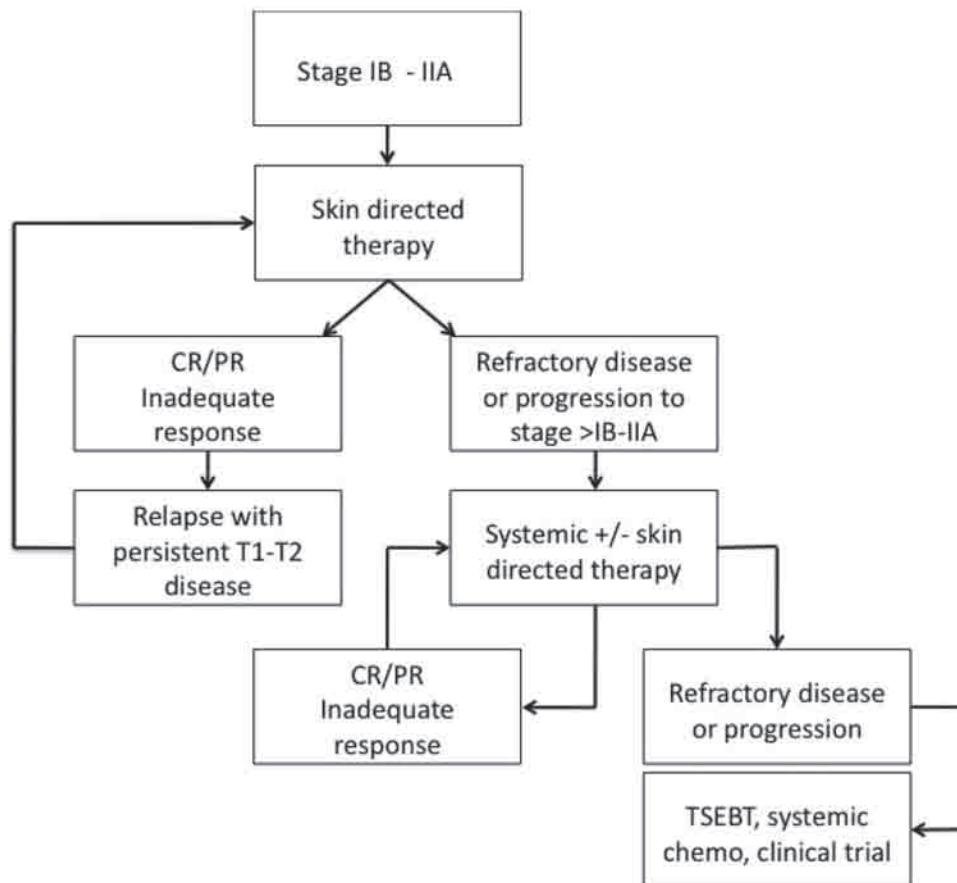
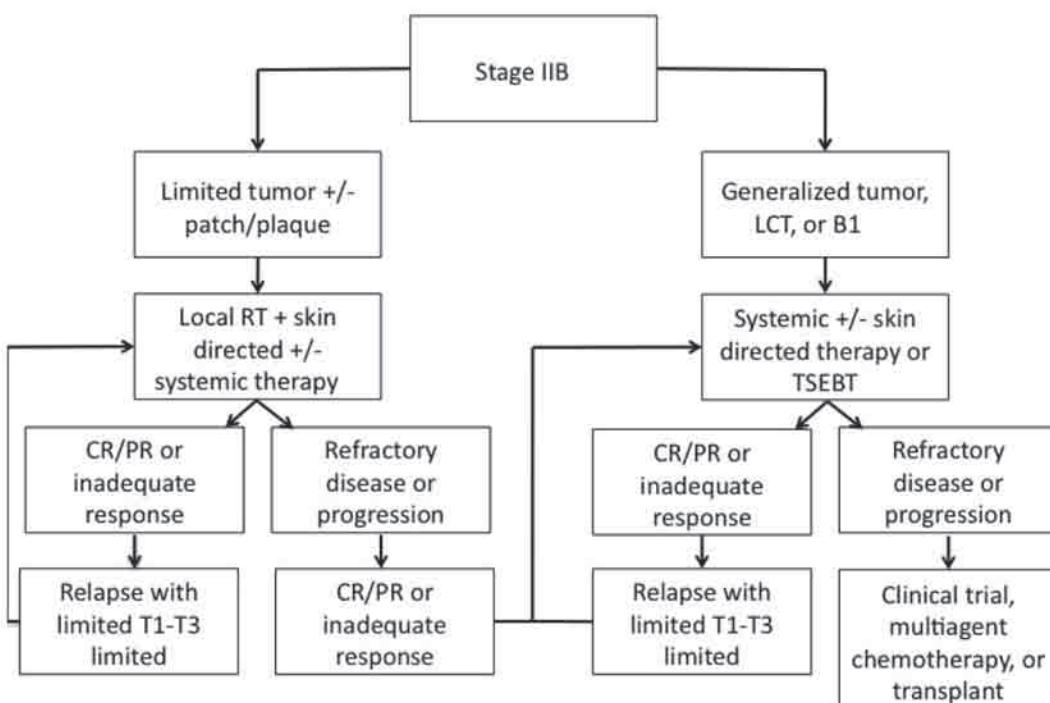


FIGURE 47-1 Therapy schematic for mycosis fungoides, IA.
CR- Complete Response; PR - Partial Response

**FIGURE 47-2** Therapy schematic for mycosis fungoides, IB-IIA.

CR - complete response; PR - partial response; TSEBT - total skin electron beam therapy

**FIGURE 47-3** Therapy schematic for mycosis fungoides, IIB.

CR - complete response; PR - partial response

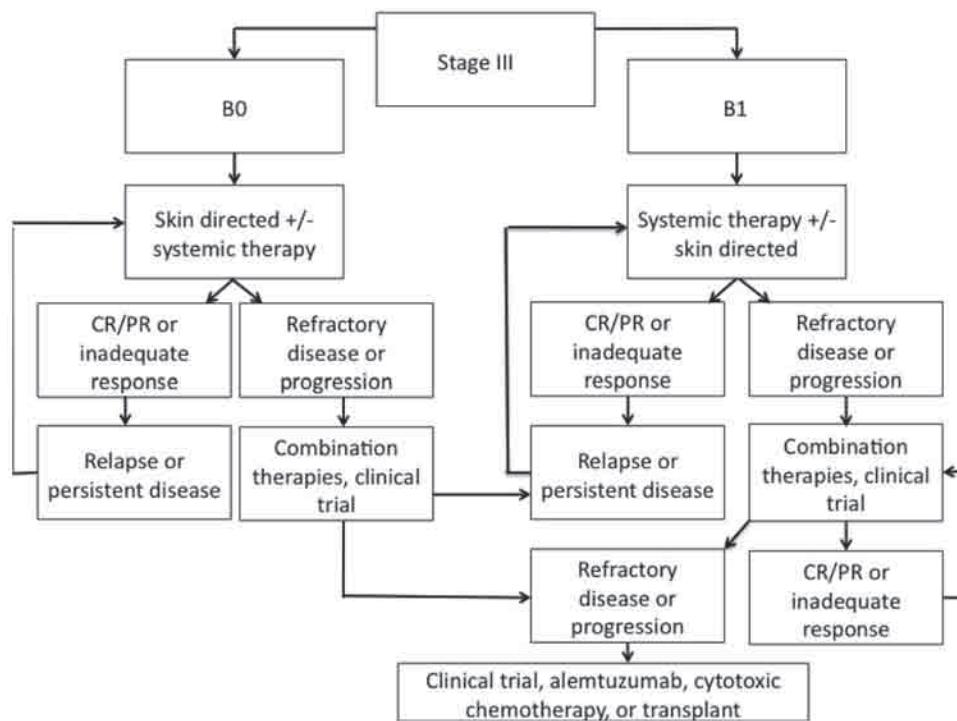


FIGURE 47-4 Therapy schematic for mycosis fungoides, III
CR - complete response; PR - partial response

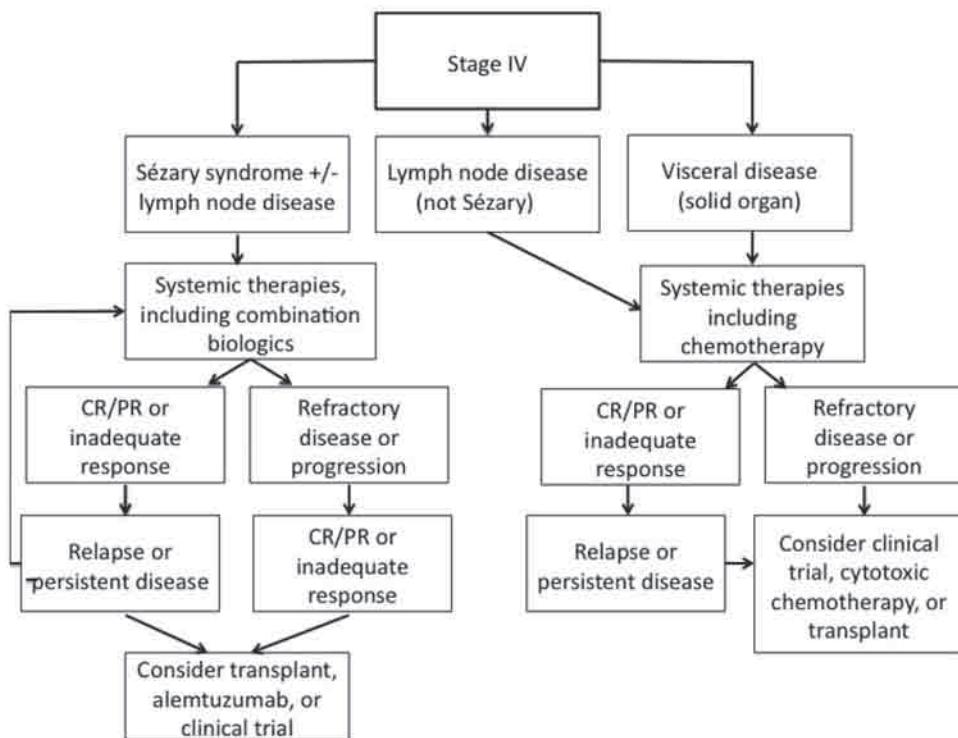


FIGURE 47-5 Therapy schematic for mycosis fungoides, IV.
CR - complete response; PR - partial response

itching. It is important to attempt to quantify the severity of pruritus using a tool such as a visual analog scale). The Visual Analog Scale is a line with the numbers one (representing minimal itch) through ten (representing the worst itch), and it is the most common assessment tool utilized

in the assessment of pruritus in clinical trials. However, a more rigorous validated tool is needed for clinical trials. The effective symptomatic treatment of pruritus is of utmost importance, especially in Sézary syndrome. Most often, occlusive medium potency topical steroids and oral

TABLE 47-1—U.S. Preventive Services Task Force: Hierarchy of Evidence¹⁵**Hierarchy of Research Design**

I	Evidence obtained from at least one properly randomized controlled trial.
II-1	Evidence obtained from well-designed controlled trials without randomization.
II-2	Evidence obtained from well-designed cohort or case-control analytic studies, preferably from more than one center or research group.
II-3	Evidence obtained from multiple time series with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of the introduction of penicillin treatment in the 1940s) could also be regarded as this type of evidence.
III	Opinions of respected authorities, based on clinical experience, descriptive studies and case reports, or reports of expert committees.

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

anti-itch measures such as gabapentin and mirtazapine are used.¹⁶

Combination chemotherapy is generally reserved for patients with lymph node or visceral disease. Patients with advanced disease in whom primary treatment fails are candidates for potential allogeneic stem cell transplantation. There is no evidence that early aggressive systemic therapy is better than conservative therapy in the management of limited disease. There is a definite need for more reliably effective therapies, especially in advanced cases of the disease. As a result, participation in clinical trials is critical for patients with advanced disease who have failed primary systemic therapies. It is important to consider allogenic stem cell transplant in patients with advanced disease as this may offer a long lasting remission or possible cure.

SKIN-DIRECTED THERAPIES

Despite advances in treatment for MF and SS, traditional skin-directed therapies are still used as the primary therapeutic modality in the majority of patients with stage I-IIA

disease (Tables 47-2 thru 47-5). In patients where initial skin-directed therapy has failed or in those with severely symptomatic disease, skin-directed therapies can be combined with systemic treatments, or the patients may be referred for experimental therapy.

TOPICAL CORTICOSTEROID THERAPY

Topical steroids can be used either as primary treatment in patients with limited patch or thin plaque disease, or they can be combined with other skin-directed treatments for added symptomatic control.² The rationale for use of corticosteroids in MF is that they inhibit lymphocyte binding to endothelium and intercellular adhesion.¹⁷ In addition, they also induce apoptosis of neoplastic lymphoid cells.¹⁸

For patients with very limited skin involvement, topical corticosteroids can be a very cost-effective option for disease control. Application of topical steroids as treatment is generally performed once to twice a day to affected areas¹⁹ (Table 47-3). The efficacy of topical steroids is not

TABLE 47-2—Stage IA-IIA

Treatment	Author/Citation	Type of Study	Level of Evidence	N	Stage	Outcome Measures
Expectant Policy	Kim ⁹ 1996	Retrospective cohort study	II-2	122	IA	Survival of T1 group similar to that of race, age, sex-matched population. Relative risk of death 0.8 (95%CI, 0.4-1.1)
	Zackheim ⁶ 1999	Retrospective cohort study		67	T1	Survival comparable to general population
				151	T2	Relative survival at 10 yrs compared to control population 67.4%
	Van Doorn ¹⁰ 2000	Retrospective Cohort Study	II-2	89	IA	5 and 10 year disease specific survival 100% and 97%
				135	IB	5 and 10 year disease specific survival 96% and 83%
				18	IIA	5 and 10 year disease specific survival 68% and 68%

TABLE 47-3—Primary Therapies in Stage IA-IIA: Topical Medications

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Topical Corticosteroids	Zackheim ¹⁹ 1998	Prospective study, open label	II-1	Twice daily application continued one month post clearance	IA (T1) IB (T2)	51 28	OR 94%, CR 63% OR 82%, CR 25%	All patients with a CR had patch disease only.
Nitrogen Mustard (NM)	Kim ²⁰ 2003	Retrospective cohort study	II-2	Aqueous and ointment based NM 20-40 mg% applied daily until 6 months post clearance IIA (T2)	IA (T1) IB (T2)	107 74 14	OR 93%, CR 65% DOR 12 mos for CR (range 1-55 mos) OR 72%, CR 41% DOR 12 mos for CR (range 1-55 mos)	
	Ramsay ²⁵ 1988	Retrospective cohort study	II-2	NM (10 mg in 60 mL) applied daily until 6 months post clearance	I	63	CR at 2 years 75.8% Median time to response: 6.5 mos; FFR: 66 mos	The definition of stage I was erythematous patches and stage II as infiltrated plaques
	Vonderheid ⁹³ 1989	Retrospective cohort study	II-2	NM 10-20 mg% aqueous solution applied daily until 2 wks after clearance. Frequency then diminished to qo/day thereafter	IIA IIA	44 89	CR 44.6% Median time to response: 41.1 mos; FFR: 44 mos CR 80% FFR at 4 yrs 37%, at 8 yrs 20% CR 68% FFR at 4 yrs 9%, at 8 yrs 4% CR 61% FFR at 4 yrs 9%, at 8 yrs 4%	
BCNU	Zachheim ²¹ 1990	Retrospective cohort review	II-2	Applied 10 mg/day for 6-12 weeks	IA IB IIA	49 66 46	OR 98%, CR 86% Median time to CR 9 wks (range 3-57) OR 84%, CR 47% Median time to CR 11.5 wks (range 6-78) FFR 17.5% OR 91%, CR 55% Median time to CR 12 wks (range 6-104) FFR 9.7%	
Bexarotene 1% gel	Heald ³⁵ 2003	Open-label, Phase III trial	II-1	Apply to lesions qo/day and increase at 1 wk intervals to 1-4x/day for total of 16 wks	IA IB IIA	25 22 2	OR 64% OR 50% OR 0%	The following were analyzed for all stages: Projected median time to response 142 days. Overall relapse rate 26%. Median DOR 214.5 days.

TABLE 47-4—Primary Therapies in Stage IA-IIA: Phototherapy

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
BBUVB	Ramsay ⁹⁴ 1992	Retrospective cohort review	II-2	Administered 3x/week until CR; treatment varying decreases in treatment during maintenance	I II	30 4	CR 83% Median time to CR: 5 mos; DOR 22 mos OR 0%	The definition of stage I was erythematous patches and stage II as infiltrated plaques
NBUVB	Clark ⁹⁵ 2000	Case series	II-3	Administered 3x/wk until clearance or minimal residual activity	IA IB	4 4	CR 75% Mean time to CR: 9 wks DOR 20 mos Mean tx to CR 26	Stages IA and IB analyzed together
	Gathers ⁹⁶ 2002	Case series	II-3	Administered 3x/wk until clearance and continued for 8 wks; maintenance with 2x/wk for 4-8 wks; then 1x/wk for 4-8 wks and then discontinued	IA IB	12 12	CR 54.2% Mean tx to CR 52.2 Mean dose 96.7 +/- 72.1 J/cm ² Mean time to relapse 12.5 wks	Stages IA and IB analyzed together
NBUVB vs. PUVA	Diederer ³² 2003	Retrospective cohort review	II-2	Administered 2x/wk for 2-37 mos (mean 11 mos) then 2x/wk for 2-66 mos (mean 14 mos)	IA/IB (PUVA) IA/IB (nbUVB)	35 21	CR 71% Mean dose to CR 283.2 J/cm ² (range 20-1760) CR 81% Mean dose to CR 31.8 J/cm ² (range 21-62.8)	
	Hermann ⁹⁷ 1995	Retrospective cohort study	II-2	Administered 2-3x/wk until clearance; then 1x/wk for 2-6 wks, then 1x/2wks for 8 wks, then 1x/3wks for 12 wks, then monthly indefinitely for maintenance	IA IB	19 49	OR: 95%; CR 79% Mean cumulative dose to clearance: 134 (55-292) J Median time to response: 3 (1-55) mos FFR at 2 years 67%, 5 yr 58% OR: 94%; CR 59% Mean cumulative dose to clearance: 140 (18-378) J Median time to response: 2 (1-36) mos FFR 2 yr 41%, 5 yr 25%	

(Continued)

TABLE 47-4—Primary Therapies in Stage IA-IIA: Phototherapy (Continued)

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
PUVA	Honigsmann ⁹⁸ 1984	Prospective single arm study	II-1	Administered 4 x/wk until clearance; then 2x/wk for 1 month, then 1x/wk for 1 month	IA	9	CR 100% Mean DOR 20 mos FFR at 44 mos 55% CR 100% Mean DOR 17 mos FFR at 44 mos 39%	Only patients with CR analyzed
	Querfeld ²⁹ 2005	Retrospective cohort review	II-2	Administered 2-3x/wk until clearance; frequency then reduced for maintenance (1x/wk – 1x/6 wks) All patients followed for 94 mos and analyzed in two groups: those who maintained response (non-relapsed) and those who did not (relapsed)	IA	39	Non-relapsed group: Median time to CR 4 mos Mean dose for CR 198 J/cm ² (29-1900) Relapsed group: Median time to CR 2 mos Mean dose for 116 J/cm ² (32-516) non-relapsed group:	Only compete responders analyzed
					IB	22		
					IIA	5	Median time to CR 4 mos Mean dose for CR 166 J/cm ² (45-392) Relapsed group: Median time to CR 2 mos Mean dose for CR 94 J/cm ² (18-286)	

TABLE 47-5—Primary Therapies in Stage IB-IIA: TSEBT

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
TSEBT	Jones ³⁸ 1995	Retrospective cohort review	II-2	TSEBT at 35 Gy (6 field technique) administered over 8-10 wks	T1	27	CR: 97% RFS: 73% (2.5 yrs), 56% (5 yrs) OS: 83% (10 yrs)	
					T2	44	CR: 75% RFS: 35% (2.5 yrs), 25% (5 yrs) OS: 57% (10 yrs)	
TSEBT	Jones ⁹⁹ 2003	Retrospective cohort review	II-2	TSEBT at 30-36 Gy administered over 8-10 wks	IA	123	CR: 95% PFS (15 yr): 50% (10 yrs)	Stage IB not analyzed separately
					IA/IB	462	CR: 90%, OR: 100% PFS (15 yr): 25%	
TSEBT +/- nitrogen mustard (NM) vs NM alone	Chinn ¹⁰⁰ 1999	Retrospective cohort review; CCT	II-2	NM alone vs TSEBT >30Gy +/- adjuvant NM following CR to TSEBT course	T2 (NM)	54	CR: 39% OS 10.7 yrs FFR (1 yr): 41%	TSEBT + NM had higher FFR ($p = 0.068$)
					T2 (TSEBT)	38	CR: 66% OS: 12.2 yrs FFR (1 yr): 39%	
					T2 (TSEBT + NM)	17	CR: 100% OS: 7.8 yrs	

diminished over time and can be used again in the event of disease relapse. The benefit is that topical steroids can be used again for relapse of disease. However, long-term use of topical corticosteroids in any disease may lead to epidermal atrophy, striae, dyspigmentation, and steroid addiction. In particular, clinical morphologic subsets of MF, such as the poikilodermatous MF, may make it difficult to interpret resolution of disease when topical steroids are used. In this variant, the clinical findings of telangiectasias and atrophy are the same as the side effects induced by prolonged use of topical corticosteroids. Hence, caution should be used in interpretation of disease versus side effect of therapy.

TOPICAL CHEMOTHERAPY

Topical nitrogen mustard (mechllorethamine hydrochloride) is the major form of topical chemotherapy used for MF and SS.²⁰ Topical carmustine (BCNU) has also been used (Table 47-3).²¹

Nitrogen mustard is the most widely utilized topical chemotherapeutic agent for MF because of its well-demonstrated efficacy, safety, and ease of application. The mechanism of action of nitrogen mustard in MF is unclear but may be mediated by immune mechanisms (e.g.,

immune stimulation) or by interaction with the epidermal Langerhans cell.²⁰

Topical nitrogen mustard preparation is applied to the skin once daily as initial therapy. If the disease is localized, the application field may be limited to the regional area of involvement or to the entire skin surface for those patients with generalized skin involvement. The initial concentration used is usually 20 mg%. If there is no response or a suboptimal response after several months of treatment, the concentration can either be increased to 30 or 40 mg% or the frequency of application may be increased to twice a day. Once complete skin clearance is achieved with topical nitrogen mustard, a maintenance regimen of some kind is usually instituted, but there is no evidence that more prolonged maintenance is beneficial.²⁰

Both acute and chronic complications have been associated with topical nitrogen mustard therapy. The most frequent acute complication is an immediate or delayed cutaneous hypersensitivity reaction. It occurs in less than 10% of patients treated with the ointment-based preparation of nitrogen mustard. However, patients can be desensitized with a variety of topical or systemic desensitizing regimens.^{20,22}

Chronic use of topical nitrogen mustard is not associated with increased risk of secondary cutaneous malignancies.²⁰ However, in patients who have used topical

TABLE 47-6—Therapy Options in Refractory Disease or the Presence of Poor Prognostic Factors in MF Stages IB-IIA

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Oral Bexarotene	Duvic ⁵¹ 2001	Phase II/III trial, open-label; CCT	I	Randomized to low dose, high dose and optimal dose (300 mg/m ²)	I A IB II A	4 22 3	OR 50% OR 52% OR 67%	For Stages IA-IIA; DOR not reached after 73 wks Median time to response 8.1 wks
Interferon - alpha	Olsen ¹⁰¹ 1989	Prospective trial, open-label	I	3 or 36 MU IM x 10 wks	I A, IB, II A	12	OR 58%, CR 8% Mean time to OR 8 wks (2-10) Mean time to CR 21 wks (7-47) Mean DOR for PR 14 wks (2-52)	
Methotrexate	Zackheim ¹⁰² 2003	Retrospective cohort review study	II-2	Median dose 25 mg PO and IM	T2	60	OR 33%, DOR 15 mos	
Denileukin Diftox	Olsen ⁵³ 2001	Phase III, randomized trial; CCT	I	Randomized to 9ug/kg/day or 18ug/kg/day x 8 courses	IB II A	14 14	9ug/kg/day; OR 43% 18ug/kg/day; OR 33% Median time to response 6 wks (3-27) DOR 6.9 mos (2.7 to 46.1 mos)	
Romidepsin	Kim ¹⁰³ 2010	Phase 2, open-label trial	II-1	14 mg/m ² on days 1, 8, and 15 of a 28 day cycle	IB/II A	28	OR 25%, CR 4%	
Tazarotene 0.1% gel	Apisarnthanarak ³⁶ 2004	Open-label, prospective pilot study	II-1	Applied to lesions once daily for 24 wks	IA/IB	19	OR & PR: 58%	Low to mid potency topical steroids allowed for alleviation of irritation
Imiquimod 5% cream	Deeths ¹⁰⁴ 2005	Preliminary open-label prospective study	II-3	Applied to lesions 3x/wk for 12 wks	IA-II B	6	50% has histologic clearance of index lesions.	The same patients had significant improvement in the clinical scores for all treated lesions

TABLE 47-7—Recommendations for MF Stage IB-IIA: Combination Therapies

Treatment	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
IFN alpha + PUVA	Chiarioti-Silenti ¹⁰⁵ 2002	Phase II trial, open label	II-1	12 MU IFN alpha administered 3x/wk with PUVA 3x/wk	I A I B II A	6 37 3	CR 74.5% (95% CI, 56.3-92.9%) Median Time to response (CR): 7 mos (1-17) DOR 32 mos (5-57) Overall survival (5 yr) 91% Relapse Free Survival 75%	
Interferon-alpha + acitretin vs. Interferon-alpha + PUVA	Stadler ¹⁰⁶ 1998	Prospective study, randomized; CCT	I	Randomized to combination therapy with Interferon alpha 9MU SQ TIW + acitretin 50 mg po qday vs. Interferon 9MU SQ TIW with PUVA TIW	Stage I	33	Interferon + acitretin OR 64.1%; CR 48.5% Median time to response 12.6 wks	Results were in stage II were not separated into stage II A and stage II B.
					Interferon + acitretin	31	Interferon +PUVA Stage I OR 86.1%; CR 83.9% Median time to response 10.9 wks	
					Interferon +PUVA	9	Interferon +actitretin OR 44.4%; CR 0% Median time to response 12.6 wks	
					Stage II	9	Interferon +PUVA OR 55.5%; CR 22.2% Median time to response 10.9 wks	
					Interferon + PUVA	9	Plaque MF	PUVA CR 72% RepUVa CR 73%
PUVA + Retinoids	Thomsen ¹⁰⁷ 1989	Retrospective cohort review	II-2	PUVA administered +/- systemic retinoids (repUVA)		69		Lower UVA dose needed than in PUVA alone
PUVA + Bexarotene	Singh ¹⁰⁸ 2004	Case Series	II-3	Bexarotene 300 mg po qday and PUVA TIW	IA-II B	8	OR 75%, CR 63%	Authors note quick relapse after either PUVA or bexarotene dose reduced

TABLE 47-8—Primary Therapies for MF Stage IIB

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
IFN alpha	Jumbou ¹⁰⁹ 1999	Retrospective study	II-2	3-6 MU SQ administered daily x 1 month then 3x/wk	IIB	31	CR 74%, CR 42% Mean time to CR 4 mos; Mean FFR 7.5 mos	Rare to have CR after 6 mos
Interferon-alpha + PUVA	Chiarioti-Silini ¹⁰⁵ 2002	Phase II trial, open label	II-3	IFN-alpha 12MU/TW with PUVA 3x/wk	IIB	3	CR 74.5% (95% CI, 56.3-92.9%) Median time to CR 7 mos (1-17) Median DOR 32 mos (5-57)	Response data not separated by stage
Vorinostat	Olsen ⁶¹ 2007	Phase IIB trial, open label	II-1	400 mg administered daily	IIB	19	CR 22.7% (95% CI, 2.8-45.4%) Median time to response: 56 days DOR >185 days	
Romidepsin	Kim ¹⁰³ 2010	Phase 2, open-label trial	II-1	14 mg/m ² on days 1, 8, and 15 of a 28 day cycle	IIB	21	CR 43%, CR 9%	
Piekarsz ⁶⁴ 2009	Phase II trial, open label	II-1	14 mg/m ² IV administered x4 wks	IIB	15	CR 46.7% Median TTR 2 mos (1-6mos) DOR 13.7 mos		
Bexarotene	Duvic ¹¹⁰ 2001	Phase II/III trial, open-label	II-1	300 mg/m ² and higher administered daily	IIB	40	>300 mg/m ² /day: CR 45%, Median time to response 180 days (14 to 197) Median time to relapse 299 days >300 mg/m ² /day: CR 55%, Median time to response 59 days (22-169) Median time to relapse 385 days	
TSEBT	Jones ³⁸ 1995	Retrospective cohort review	II-2	TSEBT at 35 Gy (6 field technique) administered over 8-10 wks	T3	17	CR: 35% RFS: 7% (2.5 yrs), 2% (5 yrs) OS: 18% (10 yrs)	
	Jones ³⁹ 2003	Retrospective cohort review	II-2	TSEBT at 30-36 Gy	>IIB	178	CR: 60%, OR 100% PFS: 10% (15 yrs)	Stages >IIB analyzed together
TSEBT +/- nitrogen mustard (NM) vs NM alone	Chinn ¹⁰⁰ 1999	Retrospective cohort review; CCT	II-2	NM alone vs TSEBT >30Gy +/- adjuvant NM following CR to TSEBT course	T3 (NM)	54	CR: 39% OR: 100% OS: 10.7 yrs	
					T3 (TSEBT +/- NM)		CR: 44% OR: 100% OS: 10.9 yrs	

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

TABLE 47-9—Primary Therapy for Patients with MF Stage IIB and Poor Prognostic Factors

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Gemcitabine	Zinzani ⁸⁰ 2000	Phase II trial, open label	II-1	1200 mg/m ² administered 3/4 weeks	IIB/III	30	OR 70% CR 10% PR 60% DOR (CR only) 15 months. DOR (PR only) 10 months.	Results not separated by stage
Doxorubicin	Wollina ¹¹¹ 2003	Retrospective, multicenter; CCT	II-2	20 mg, 20–30 mg, or 40 mg/m ² IV administered 1–2x/month.	IA-IVB	34	OR 85%, CR 41%, PR 44%. Median Overall (IIB to IVB) 17+–12.2 months. Overall event free survival 12+–9.5 months, disease free survival 13.3 +–10.5 months.	Results not separated by stage

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

nitrogen mustard in combination or sequentially with other skin-damaging therapies (e.g., ultraviolet [UV] phototherapy, radiation therapy), there is an increased risk for nonmelanoma skin cancers.^{23,24} Application of nitrogen mustard in the genital areas should be strictly avoided since genital application has been linked with development

of secondary skin cancers. Topical HN2 can be used safely in pediatric patients, and studies have not shown worse adverse effects in children.²⁰ There is no evidence of significant systemic absorption of the medication.

BCNU can be used in solution or ointment form.^{21,25} Similar to nitrogen mustard, it can be applied to regional

TABLE 47-10—Secondary Therapies for MF Stage IIB

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Denileukin Diftitox	Olsen ⁵³ 2001	Phase III trial, randomized; CCT	I	Randomized to 9 ug/kg/day or 18 ug/kg/day for 8 courses	IIB	9 ug/kg/day: 9 18 ug/kg/day: 10	OR of 11% at 9 ug/kg/day; CR 0% OR of 50% at 18 ug/kg/day, CR 20% Median time to response 6 wks (3-27) DOR 6.9 mos (2.7 to 46.1 mos)	Median time to response and DOR included all patients with response
Pentostatin	Kurzrock ¹¹² 1999	Prospective study, open label	II-3	5 mg/m ² for 3 consecutive days of 3 week cycle	IIB	6	OR 66%, CR 17% DOR 2 mos	
Temozolomide	Tani ⁸² 2005	Phase II study, open label	II-3	150 mg/m ² /day po for 5 days x 1 cycle; 200 mg/m ² /day po for 5 days x 2 cycles	IIB/III	9	OR 33%, CR 11%	Results not separated by stage

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

TABLE 47-11—Primary Therapies for MF Stage III

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Methotrexate	McDonald ¹³ 1978	Retrospective review	II-3	60-249 mg/m ² IV administered qweek with oral citrovorum	II, III	11	CR 64%	CR sustained with weekly low dose methotrexate (25-50 mg)
ECP +/- biologic therapy	Zackheim ⁷⁹ 1996	Retrospective review	II-3	5-125 mg/wk administered weekly (oral)	T4	29	OR 58%, CR 41% DOR 31 mos Median overall survival was 8.4 yrs.	Results not analyzed by stage (i.e., those with blood and lymph node involvement were not analyzed apart from those without involvement)
Bexarotene	Duvic ¹¹⁰ 2001	Phase II/III trial, non-randomized	II-1	300 mg/m ² /day and higher	III	29	300 mg/m ² /day: OR 32% Median time to response 180 days (14 to 197) DOR 299 days At >300 mg/m ² /day: OR 55% Median time to response 59 days (22-169) DOR 385 days	Photopheresis monotherapy: OR 75%, CR 38% Combination biologic therapy: OR 84%, CR 20%
IFN alpha	Jumbou ¹⁰⁹ 1999	Retrospective review	II-3	3-6 MU SQ administered daily x 1 month then 3x/wk	III	11	OR 25%, CR in (III-IV) 16.5%. Mean time to response (CR only) 4 mos DOR 7.5 months Relapse rate 57%	CR rare after 6 mos

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

TABLE 47-12—Secondary Recommendations for MF Stage III

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Stage	N	Outcome Measures	Comments
Alemtuzumab	Kennedy ⁷⁷ 2003	Phase II trial, open label	II-3	30 mg IV administered 3x/wk for 12 wks	IIB	5	For all stages: OR 38% DOR less than 3 months.	Results not separated by stage
								Time to progression was short, with all patients developing PD within 4 months of starting medication
Gemcitabine	Zinzani ⁸⁰ 2000	Phase II trial, open-label	II-1	1,200 mg/m ² administered (3/4 weeks) x 3 cycles	IIB/III	30	OR 70%, CR10%, Median DOR for CR 15 mos, and PR 10 mos	Results not separated by stage
2-chloro-deoxyadenosine (2-CdA)	Kuzel ¹¹⁵ 1996	Prospective trial, open-label	II-3	0.1 mg/kg/d administered x 5 days. Cycles administered at 28-day intervals	III	5	CR 20%, PR 20% DOR (CR only) 4.5 months DOR (PR only) 2 months	

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

areas for localized disease or to the entire skin surface for generalized disease. Contact should be avoided with the eyes or orifices.²⁶ There are both cutaneous and hematologic side effects. The majority of patients experience a degree of erythema accompanied by a burning sensation. This tends to localize to the intertriginous areas. It usually subsides with the use of topical corticosteroids and cool compresses. More severe erythematous reactions can lead to the development of telangiectasias that can persist for several years. With respect to hematologic parameters, 5% of patients treating the general body surface had mild leukopenia. Other adverse hematologic side effects have not been observed.²⁶

Topical corticosteroids, nitrogen mustard, and BCNU are indicated as initial primary therapy for patients with stage IA or IB disease. Topical chemotherapy should be considered as an alternative for those patients who are candidates for phototherapy but prefer the convenience of home application or already have a significant amount of photodamage.

PHOTOTHERAPY

Phototherapy involves using UV radiation in the form of UVA or UVB wavelengths. It can be used alone or in

combination with psoralen, a photosensitizing agent. Psoralen used with UVA (PUVA) is also referred to as photochemotherapy. PUVA therapy is widely used in dermatology for various dermatoses such as psoriasis. Psoralens intercalate between pyrimidines within DNA and, upon exposure to UVA, form photoadducts and DNA crosslinks.²⁷ This process results in cytotoxic, antiproliferative, and immunomodulatory effects. The long-wave UVA has an advantage over UVB because of its greater depth of penetration. This is useful in that while MF is defined as an epidermotropic process, a considerable amount of neoplastic infiltrate is still in the dermis.

Phototherapy used with UVA is indicated as primary therapy in generalized plaque and erythrodermic MF without evidence of extracutaneous disease (Table 47-4). It is also used as palliative therapy in combination with another treatment in patients with advanced disease. Initially, PUVA treatments are given 2-3 times per week, with a minimum of 48 hours between treatments to monitor the delayed erythema reaction.²⁸ The initial dose of UVA and the rate at which the dose is increased are generally dependent upon the skin type. Erythrodermic patients tend to require very low starting doses with very small dose increments. After maximal response, the frequency of PUVA treatments is decreased.

TABLE 47-13—Recommendations for the Treatment of MF IVA/IVB (Not Sézary Syndrome)

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Definition of Response	N	Outcome Measures	Comments
Bexarotene	Duvic ¹¹⁰ 2001	Phase II-III study; non-randomized	II-1	300 mg/m ² /day or higher daily	Skin and lymph node regularly assessed; CCR 100% clearance of disease; PR – 50% improvement; both confirmed after 1 month	IVA – 15 IVB - 9	At 300 mg/m ² /day: OR for VA 44%, OR for IVB 40% Median time to response 180 days DOR 299 days % relapse 36% >300 mg/m ² /day not given by stage. OR 55% Median Time to Response 59 days DOR 395 days % relapse 38%.	Used Physician's Global Assessment of Clinical Condition (PGA) and considered skin, lymph nodes and other disease manifestations – no specific criteria for definition of CCR or PR
Denileukin Difitox/Diftitox	Olsen ³³ 2001	Phase III trial, randomized study; CCT	I	Randomized to 9 ug/kg/day or 18 ug/kg/day for 8 courses	Skin, lymph node and blood assessed; CCR clinical clearance but histologic no verified; PR >50% reduction in tumor burden	IVA: 7 treated with 9 ug/kg/day; 8 treated with 18 ug/kg/day	9 ug/kg/day: OR 14%, CR 0% 18 ug/kg/day: OR of 25%, CR 13% Median time to response 6 wks (3-27) DOR 6.9 mos (2.7 to 46.1 mos)	Criteria for CR and PR not clearly defined
IFN-alpha	Olsen ¹⁰¹ 1989	Randomized Prospective Study; CCT	III	Randomized to 3 or 36 MU IFN-alpha 2a daily for 10 wks	Change in cutaneous and/or nodal disease by physical examination. Blood assessment included. CR complete clearance of disease and PR greater than 50% diminution in measurable disease	IVA - 2	Both treated with 36 MU and with CR lasting 14 mos and 27.5 mos	Criteria for CR and PR not clearly defined
Vorinostat	Duvic ⁶³ 2007	Phase II study, randomized; CCT	I	400 mg qd or 300 mg bid x 3 d/wk x 4 wk, then 5 d/wk or 300 mg bid x 14 d with 7 d rest	Skin, blood, lymph node. CCR 100% clearance of disease; PR – 50% improvement; both confirmed after 1 month	IVA – 10 IVB - 8	OR 25%, CR 0% Median time to response 11.9 wks DOR 15.1 wks	Efficacy done for patients with IIIB and higher disease states
	Olsen ⁶¹ 2007	Phase IIIB study, open-label	II-1	400 mg oral/day	Skin only. CR 100% clearance of skin. PR >50% reduction in skin disease	IVA – 18 IVB - 4	OR 29.5%, CR 0% Median time to response 56 days DOR 80.8 (48+-418+days)	Efficacy done for patients with IIIB and higher disease states

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Definition of Response	N	Outcome Measures	Comments
Romidepsin	Piekartz ⁶⁴ 2009	Phase II, open-label	II-1	14 mg/m ² days 1, 8, 15 of 28-day cycle	CR – clearance of disease at all known sites. PR – response in skin or lymph nodes	IVA – 28 IVB – 13	IVA: OR 18%, CR 7% IVB: OR 31%, CR 8% Median time to response 2 mos (range 1-6 mos) DOR 13.7 mos Median time to progression 15.1 mos	
	Kim ¹⁰³ 2010	Phase II, open-label	II-1	14 mg/m ² days 1, 8, 15 of 28-day cycle	CR – clearance of disease at all known sites. PR – response in skin or lymph nodes	IVA-24	OR 33%, CR 8% DOR 15 mos Time to response for OR 2 mos Time to response for CR 4 mos	
Bortezomib	Zinzani ⁸⁴ 2007	Phase II study, open label	III	1.3 mg/m ² day 1,4, 8, 11 followed by 1 wk rest (one cycle), Tx for 6 cycles	CR complete absence of disease in skin, lymph nodes, blood, and bone marrow and confirmed for 1 month. PR decrease of 50% or more from baseline in skin and lymph nodes (international criteria – J Clin Oncol 1999; 17: 1244-53	6	OR 70%, CR 10%	Responses not given by stage
2-chlorodeoxyadenosine	Kuzel ¹¹⁵ 1996	Phase II study, open-label	II-3	2-CdA 0.1 mg/kg/day for 5-7 days IV on 28 day intervals for 6 cycles on until CR	CR – absence of disease in skin, lymph nodes, and blood; PR – 50% reduction in skin or nodal disease	IVA – 8 IVB - 2	One CR in IVA. Remainder of the IVA/IVB patients with no response	Response not given by stage
Gemcitabine	Jidair ¹¹⁶ 2009	Retrospective cohort study	III	Gemcitabine 1000 mg/m ² days 1,8,+/- 15 of a 21 or 28 day cycle	Skin assessed alone. CR – clearance of all skin lesions. PR – 50% reduction in skin tumor burden	IV - 5	OR 78%, CR 11%	Responses not given by stage
Duvic ¹¹⁷ 2006	Phase II study, open-label		II-1	Gemcitabine 1000 mg/m ² days 1,8, 15 > 6 cycles	Skin, lymph node, blood. CR – clearance of all skin lesions. PR – 50% reduction in tumor burden	IVA – 7 IVB – 8	IVA - OR 71%, CR 14% IVB – OR 88%, CR 0% Median overall survival for all patients 20.4 mos 3-year OS 28% (95% CI, 17-46%)	

(Continued)

TABLE 47-13—Recommendations for the Treatment of MF IVA/IVB (Not Sézary Syndrome) (Continued)

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Definition of Response	N	Outcome Measures	Comments
Combination VICOP-B	Fierro ¹¹⁸ 1997	Prospective study, open label	II-1	12 week regimen of VICOP-B	CR – clearance of all clinical disease for 4 weeks; PR – >50% decrease in disease for 4 weeks	IVA – 13 IVB – 4	IVA – OR 69%, CR 38% IVB – OR 75%, CR 25% DOR 7.3 mos (range 1-49 mos). Median time to progression 6.8 mos (range 3-51 mos)	No clear criteria given for PR or specification as to compartments evaluated in global assessment
Doxorubicin	Wol-lina ¹¹⁹ 2001	Retrospective cohort study	II-2	20-40 mg/m ² 1-2x/month as tolerated	CR – clearance of all clinical disease for 4 weeks; PR – >50% decrease in skin disease for 4 weeks	IVA – 12	OR 83%, CR 25% Mean survival for stage III-IV 14.6 months (SD 8.6mos)	No clear criteria for PR for compartments other than skin.

CR complete response; PR partial response; OR overall response

TABLE 47-14—Primary Therapies for Sézary Syndrome

Treatment Modality	Author	Study Details	Treatment Regimen	Definition of response	N	Outcome Measures	Comments
Extracorporeal Photopheresis Monotherapy (ECP)	Edelson ⁴² 1987	Prospective cohort study	II-1	ECP q4wks	25% reduction in skin score from baseline	37 OR 73% OR included 24 of 29 with exfoliative erythroderma. Mean time to response: 22 +/- 10 wks.	Patients not sub-analyzed by T stage or overall stage. All patients had circulating atypical mononuclear cells, but the amount not defined
	Evans ⁴³ 2001	Prospective cohort study	II-1	ECP q4wks	25% reduction in skin score from baseline	23 OR 57% (25% reduction from baseline)	Reduction in skin score correlated with reduction in Sézary cell count that was statistically significant
Combination Therapy ECP + IFN- α + Bexarotene	Richardson ¹²⁰ 2006	Retrospective cohort study	II-2	ECP 2 consecutive d q mon x >6 mon + IFN α 1.5 Mu 3-5x/wk + Bexarotene 24/28 pts +/- IFN γ 40-100 Ug 3-5x/wk, acitretin GM-CSF, PUVA, top NM, top BCNU, UVB	CR – no evidence of cutaneous disease and Sézary count less than 5%; PR>50% reduction in skin disease	28 OR 89%; CR 29 CR: 2 relapse 3 & 40 mon, rest >36 mon; PR 4-24 mon	Skin disease assessed only for PR definition
ECP monotherapy vs. combination biologic therapy	Gottlieb ¹²¹ 1996	Retrospective cohort study; CCT	II-2	ECP q4wks	CR – no evidence of skin disease, and Sézary cells in blood. PR - at least 50% reduction of skin disease and circulating Sézary cells.	28 OR 71%, CR 25% DOR (CR only) not reached and PR 16 mos	Results of study not divided by stage, but majority (67.7%) had IV-A disease; 87% had >5% Sézary cells. Presence of Sézary cells in the peripheral blood was associated with a better skin response
						OR 88%, CR 44%	(Continued)

TABLE 47-14—Primary Therapies for Sézary Syndrome (Continued)

Treatment Modality	Author	Study Details	Treatment Regimen	Definition of response	N	Outcome Measures	Comments
Suchin ¹⁴ 2002	Retrospective cohort study; CCT	II-2	ECP q4wks	CR – no evidence of skin disease, and Sézary cells in blood for 3 mos. PR - at least 50% reduction of skin disease and circulating Sézary cells	Of the 47 patients, 11 had stage III, and 21 had stage IV $42 > 5\%$ circulating Sézary cells	OR 76%, CR 38%	Response rates were not stratified by disease stage. The differences in overall response rates between the 2 groups were not statistically significant ($P = .47$)
INF-alpha	Jumbou ¹⁰⁹ 1999	Retrospective cohort study	II-3	Mean 2.7 Mu qd	Skin, blood, lymph node. CR – clinical clearance of all disease; PR – $>50\%$ decrease in extent of disease	11 OR 25%, CR 16.5% Mean time to CR 4 mos Mean DOR 31 mos 57% with relapse within mean period or 7.5 mos	
Dreno ¹²² 1991	Prospective cohort study	II-1	6-9 Mu qd \times 2-3 mos then tiw \times 10 mos	CR – clearance of all disease for 4 weeks.	13	OR 23%, CR 0%	No definition given for PR
Denileukin Diftitox	Foss ⁵⁵ (date)	Retrospective cohort study	II-3	9 or 18 μ g/kg <u>plus</u> -prednisone 20 mg or decadron 8 mg \times 5 days q 3 weeks	Response based on total sum of disease in skin and blood.	8 OR 50%, CR 0%	No definition given for CR or PR
Chinn ⁵⁴ 2006	Retrospective cohort study	II-3	4-18 μ g/kg q d \times 5 first cycle <u>plus</u> -decadron 8 mg then 18-27 μ g/kg q day \times 5 <u>plus</u> decadron 8 mg q 3 wks	Skin, blood lymph node. CR complete clearance of disease; PR $>50\%$ decrease in disease at all sites	6 OR 50%, CR 0% Median time to first response 42 days (range 8-293 days) Median TTF 5 mos		

Bexarotene	Duvic ¹¹⁰ 2001	Phase II-III study, open-label	II-1	300 mg/m ² /day or higher daily	Skin and lymph node regularly assessed; CR 100% clearance of disease; PR – 50% improvement; both confirmed after 1 month	17	OR 24%; CR 0%	
Vorinostat	Duvic ⁶³ 2007	Phase II study, randomized	II-2	400 mg qd or 300 mg bid x 3 d/wk x 4 wk, then 5 d/wk or 300 mg bid x 14 d with 7 d rest	Skin, blood, lymph node. CCR 100% clearance of disease; PR – 50% improvement; both confirmed after 1 month	11	OR 36%, CR none Median time to response 11.9 wks DOR 15.1 wks	
Olsen ⁶¹ 2007		Phase IIIB study, open-label	II-1	400 mg oral/day	Skin only. CR 100% clearance of skin. PR >50% reduction in skin disease	30	OR 33 %, CR none Median time to response 31 days DOR not reached (34+-441+days)	
Methotrexate – low dose	Zackheim ⁷⁹ 1996	Retrospective cohort study	II-3	60-240 mg/m ² over 24 hr IV infusion with leucovorin rescue. Escalating dose q 5 days. Maintenance oral dose 25-50 mg/wk or 60-240 mg/m ² /wk with leucovorin rescue	CR 100% clearance of disease. PR>50% reduction in disease. Both confirmed 4 weeks later.	10	OR 40%; CR 20% DOR 31 mos	Response definitions not clear for each compartment

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFIR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

TABLE 47-15—Secondary Therapies for Sézary Syndrome

Treatment Modality	Author	Study Details	Level of Evidence	Treatment Regimen	Definition of response	N	Outcome Measures	Comments
Liposomal Doxorubicin	Quereux ⁸¹	Prospective cohort study	II-2	40 mg q4 wks for 8 cycles.	Skin only. CR – clearance of all lesions. PR – 50% decrease in number and size of lesions	10	OR 60%; CR 10% Overall PFS 5 months	
Gemcitabine	Duvic ¹¹⁷ 2006	Phase II study	II-2	D1, 8, 15 at 1000 mg/m ² ≥ 6 cycles; 3 of 8 pts treated off-study at 150 mg/m ²	Skin, blood, lymph node	11	OR 73%; CR none Median overall survival for all patients 20.4 mos 3-year OS 28% (95% CI, 17-46%)	
Chlorambucil	Winkelmann ¹²³ 1984	Retrospective cohort study	II-2	~4 mg (2-6)/d + 20 mg/d prednisone, maintenance 2-4 mg + prednisone 5-10 mg/d	Skin and blood. CR – clearance in skin and blood. PR – improvement in erythroderma and decrease of Sézary cells to 100-500 mm ³	26	OR 90% CR 35%	
Pentostatin	Kurzock ¹¹² 1999	Prospective study	II-1	5 mg/m ² for 3 consecutive days of 3 week cycle	Skin and blood. CR – clearance of all disease. PR – 50% improvement in skin score and Sézary cell count	14	OR 71%, CR 29% DOR 3.5 months	
Fludarabine	Quaglino ¹²⁴ 2004	Phase II study, open label	II-1	25 mg/m ² × 5 days q 28 days	Skin, blood, lymph node. CR – clearance of all disease. PR – 50% improvement in skin score and Sézary cell count	17	OR 35%; CR 18%	
Alemtuzumab	Querfeld ¹²⁵ 2006	Prospective cohort study and clinical use	II-1	30 mg tiw IV × 4 wks then 30 mg SQ tiw × 8 wks	Skin, blood, lymph node	17	OR 88%; CR 47% DOR 7 mos	
	Bernengo ⁷⁶ 2007	Prospective cohort study	II-1	3 mg dL1, 10 mg d3, 15 mg qod × 4 or 3 mg dL1, 10 mg tiw	Skin, blood, lymph node. CR – clearance of all disease. PR – 50% improvement in skin score and Sézary cell count	14	OR 86%; CR 21% DOR not reached	

OR, overall response rate; CR, complete response rate; PR, partial response; DOR, median duration of response; FFR, median freedom from relapse; OS, median overall survival; RFS, relapse free survival; CCT, controlled clinical trial.

Both acute and chronic adverse effects have been observed with PUVA therapy.²⁸ Nausea from psoralen ingestion is observed in 10-20% of patients and can be managed by ingesting the drug with food or milk, or with appropriate antiemetics.²⁷ Phototoxic reactions can range from erythema to the development of bullae. Ultraviolet-opaque goggles must be worn during the UVA irradiation. Long-term PUVA therapy with high cumulative doses has been linked to an increased risk for the development of squamous cell carcinomas,^{29, 30} pigmented macules,³¹ and cataract formation.²⁷ Up to one-third of patients treated with PUVA develop signs of chronic photodamage and secondary cutaneous malignancies. After each PUVA treatment, appropriate photoprotection, including application of sunscreens, protective clothing, and UV-shielding glasses, should be used for a minimum of 24 hours.

Ultraviolet B (UVB) therapy is a widely used alternative to PUVA. While broadband has been used, it has been supplanted with light limited to the 311 nm wavelength known as narrowband UVB (NBUVB). The use of NBUVB does not require the ingestion of psoralen prior to therapy, which is advantageous in patients that have problems tolerating the medication. Similar to PUVA, it is performed 2-3x per week with 24 hours between treatments. NBUVB is considered to have less toxicity than broadband UVB or PUVA because the penetration of UVB is reduced. Although several published studies using NBUVB in MF have shown clinical efficacy superior to that of broadband UVB, PUVA has been shown to be more effective than either³² (Table 47-4).

TOPICAL RETINOID AND REXINOID THERAPY

Retinoids modulate gene expression by activating nuclear retinoic acid receptors (RARs) and retinoid X receptors (RXRs). This leads to alterations in cell differentiation, proliferation, and apoptosis.³³ These properties have prompted investigation into their use as antineoplastic agents. Broad-spectrum retinoids have an affinity for RARs but exhibit poor tissue specificity and low activity. There is a derivative category of agents, known as rexinoids, which specifically activate the RXR receptors and have a lower affinity for RAR receptors. A rexinoid agent commonly used in MF is bexarotene. Although the molecular basis of bexarotene has not been clearly elucidated, it has been shown to induce apoptosis in CTCL lines.³⁴

Bexarotene 1% gel, a rexinoid, is the most commonly used topical retinoid for treating MF. The medication is typically applied as a thin film to the patches or plaques. It is most effective and best tolerated when used twice daily³⁵ (Table 47-3). Because of the irritant effect of the rexinoids, it is only feasible to use this agent when there is limited number of patches or plaques. It is not intended for generalized application. The most common toxicity of bexarotene gel is irritation at the sites of application and occurs in

the majority of patients.³⁵ The irritation commonly occurs in flexural areas affected by MF. Because of the erythema from the irritant reaction, it may be necessary to withhold therapy for a few weeks to assess disease activity.

Tazarotene 0.1% gel, a RAR agonist, has also been evaluated in a pilot study³⁶ (Table 47-6). The gel was applied daily to discrete lesions only. Use of the gel to lesions resulted in a 35% clearance rate.³⁶ Mild to moderate local irritation was the most common adverse event in the majority of patients (84%). Any associated irritation was relieved by decreasing the frequency to every other day application or the use of a mid-potency steroid.³⁶

Imiquimod

Imiquimod is a topical immunomodulator that has been approved by the Food and Drug Administration (FDA) for the treatment of genital warts. The drug is believed to function in part through the induction of local interferon (IFN) production.³⁷ Because systemic IFN is effective in the treatment of MF, it has been hypothesized that topical imiquimod might also be effective while sparing patients the systemic side effects of IFN treatment. An open-label, pilot study used 5% imiquimod cream to localized patches and plaques of MF (Table 47-6). Imiquimod was generally well tolerated, and skin irritation was limited to lesions, which ultimately cleared with treatment.

RADIATION THERAPY

Mycosis fungoides is an extremely radiosensitive neoplasm. Individual plaques or tumors can be treated with local electron beam therapy (EBT) to total doses of 24-36 Gy, with a high complete response rates.

Total skin electron beam therapy (TSEBT) has been developed to treat patients with extensive cutaneous disease.³⁸ Radiation is administered four times a week to a total dose of 30-36 Gy. The treatment course is 8-10 weeks in duration. During each treatment session, patients assume multiple positions to ensure that the entire skin surface is irradiated. Supplementary treatment is required for the soles of the feet, perineum, and inframammary areas. The eyes are shielded routinely, but other areas may be protected over the course of the treatment to help control localized skin reactions.

Short-term side effects associated with TSEBT include acute erythema, desquamation, temporary nail and hair loss, and an impaired ability to perspire properly for up to 12 months. Long-term, there is an increased risk of secondary squamous cell and basal cell carcinomas of the skin. The risk of secondary malignancies is greatest in those who have received long courses of therapy with other skin-damaging therapies such as phototherapy.²³

The use of TSEBT is indicated as primary or secondary management in patients with generalized plaque or tumor involvement (Tables 47-5 and 47-8). TSEBT can provide

important palliative benefit in patients with extensive or severely symptomatic disease. Although the therapy is effective with nearly 100% response rates, it is not curative, and disease usually recurs. Up to two courses of TSEBT may be administered over the course of a lifetime, which can limit its use in long-term management of the disease.³⁹

SYSTEMIC THERAPIES

Systemic therapies are indicated when skin-directed primary therapies fail or in aggressive or advanced MF cases. Patients with significant numbers of circulating Sézary cells should also be placed on a systemic therapy as part of their treatment regimen. Therapeutic efforts are focused on targeted biologic agents that promote apoptosis and manipulate the host immune response. Either the combination of a biologic agent with a skin directed therapy or the combination of multiple biologic agents results in improved disease control by acting in a synergistic manner. Toxicity can also be reduced in combination regimens, as lower doses are required for each therapeutic modality.

BIOLOGIC THERAPIES

Extracorporeal Photopheresis (ECP)

ECP is considered first line therapy for patients with Sézary cell blood involvement (Table 47-14). ECP delivers psoralen and UVA radiation systemically by utilizing an extracorporeal technique.⁴⁰ White blood cells are collected in a clear container (leukapheresis) and exposed to psoralen. The cells are then irradiated with UVA (PUVA). The irradiated cells are returned to the patient in a closed system. The ECP instrument performs the leukapheresis and delivers the UVA. The mechanism of action of ECP involves induction of malignant T cell apoptosis with PUVA, which is accompanied by the enhancement of a tumor-specific immune response. Extracorporeal photopheresis also induces monocytes to differentiate into dendritic cells capable of phagocytosing and processing the apoptotic tumor cell antigens.^{3,41}

A standard complete ECP regimen for CTCL consists of 2 consecutive days of therapy repeated at 2-4-week intervals. The frequency of administration is adjusted according to disease severity and/or clinical response. After a maximal, stable response has been achieved, the frequency of treatments is gradually decreased, and then stopped completely, unless the disease relapses or flares during the weaning process, or when maintenance therapy is given. Maintenance therapy is given every 4-6 weeks; a repeat attempt at weaning can be made later. If an adequate response is not attained with ECP monotherapy, or if patients have a significant level of circulating Sézary cells, additional biologic agents should be added. These can include interferon or systemic retinoid. A minimum of 4-6

months of treatment should be given before ECP is considered a failure.

An advantage of ECP is its limited side effect profile. One of the greatest advantages of ECP is that the adverse effects are minimal.⁴⁰ Common side effects include mild fatigue associated with leukapheresis and fluid shifts. Peripheral intravenous access for treatment is preferable to central access to minimize complications. There are no significant side effects in terms of laboratory parameters. Patients receive psoralen, and need to protect their eyes and skin from UV exposure for 24 hours after treatment. Extracorporeal photopheresis (ECP) has been shown to be most effective in patients with blood involvement, particularly those with SS^{42,43} (Table 47-14).

Interferon-alpha

Interferon (IFN) therapy is indicated for refractory or advanced disease and is often combined with other skin-directed or systemic therapies. IFN was originally discovered by Isaacs and Lindenmann in 1957.⁴⁴ It is a protein expressing virus nonspecific antiviral activity.⁴⁵ Based on antigenic proteins, IFNs are divided into three main groups: IFN-alpha, IFN-beta, and IFN-gamma. IFN-alpha and beta bind to IFN type I receptor while IFN-gamma binds to the IFN type II receptor. IFN-alpha preparations are primarily used in the treatment of CTCL.⁴⁶ IFN-gamma has been used rarely as an alternative in patients who have developed resistance to IFN-alpha.⁴⁶

IFN-alpha induces a variety of immunologic effects that may lead to clinical response.³ It directly enhances cell-mediated cytotoxicity by CD8⁺ T cells and NK cells, which augments the antitumor response. It also suppresses TH2 cytokine production by malignant T cells, which can lead to enhanced immunomodulation.

Interferons are administered intramuscularly or subcutaneously with a maximum plasma concentration 6 to 8 hours after administration.⁴⁶ There are multiple regimens used. Traditionally, interferon-alpha is started at lower doses, such as 1-3MU three times per week subcutaneously and titrated up as tolerated. However, because of the numerous associated side effects, it is typically not used as monotherapy. Rather, it is used in combination with ECP, systemic retinoids, methotrexate, and phototherapy in an effort to limit side effects. When used in combination, it is a first line therapy for advanced MF and SS.²

The adverse effects of interferon can prohibit its use in some patient populations such as the elderly. The most common side effects include fevers, chills, tachycardia, malaise, myalgias, and headaches that are part of the general flu-like syndrome.⁴⁷ The flu-like syndrome seems to decrease in intensity with time.⁴⁶ However, in patients on low-dose intermittent therapy, acetaminophen is able to control the symptoms. Hematologic side effects primarily involve leukocytes, platelets and erythrocytes. Leukopenia occurs within hours of exposure, and often stabilizes around

40–60% of the normal leukocyte count. The recovery of granulocyte and lymphocyte counts is rather rapid after discontinuation of IFN therapy.⁴⁷ Prolonged IFN therapy often results in normocytic normochromic anemia, which in contrast to the IFN-induced leukopenia, has a slow recovery. Thrombocytopenia is also a common side effect especially in patients with hematologic malignancies.⁴⁷

Retinoids

Systemic retinoids are indicated primarily in patients with advanced disease and can be used as monotherapy or as part of combination regimens with skin-directed or other biologic therapies (Tables 47-7, 47-8, 47-9, 47-11, 47-13). They are also used in early stage, refractory disease (Table 47-6).

The most commonly used systemic retinoid is a retinoid X receptor (RXR) agonist, bexarotene; however, retinoic acid receptor (RAR) agonists, such as isotretinoin, acitretin, or all-trans retinoic acid, are available as alternative agents.⁴⁸ Much of the molecular basis of the mechanism of action of bexarotene is unknown. However, it has been shown to induce apoptosis in CTCL lines and T lymphocytes from Sézary patients.^{34,49} In addition, patients who have responded to bexarotene had higher CD8+ cell counts after therapy.⁵⁰ The initial dose of oral bexarotene is 300 mg/m²/day, which can be adjusted according to the clinical response and the severity of adverse effects.

There is a common toxicity profile for the different forms of retinoids, and many of these adverse effects are dose dependent. Most commonly, patients experience photosensitivity and dryness of the skin and mucous membranes. Other adverse effects include myalgia, arthralgia, and fatigue, and less commonly, headaches. On rare occasions, headaches can be caused by pseudotumor cerebri. The well-known teratogenic effects of retinoids must be carefully addressed in female patients of childbearing age. Potential long-term, cumulative toxicity of retinoids includes the development of bony changes such as hyperostosis. Bexarotene also has unique effects on the pituitary-thyroid axis, which results in hypothyroidism with low free thyroxine (FT4) and low thyroid-stimulating hormone (TSH) levels.

Bexarotene is a selective agonist for RXR receptors. The receptors can form homodimers and heterodimers with RARs, as well as with other nuclear receptors such as vitamin D receptors and thyroid receptors. Due to the formation of heterodimers, the use of bexarotene affects the thyroid receptors leading to central hypothyroidism. Because of their potential hepatotoxic and hyperlipidemic effects, liver function and serum lipid levels (triglycerides/cholesterol) should be monitored during treatment. Bexarotene also has more profound effects on serum lipid levels, especially triglycerides, than any other retinoid. Thus, it is conventional to have patients on lipid-lowering agents and thyroid supplements during bexarotene therapy.

These are ideally started in the week prior to beginning bexarotene therapy. Gemfibrozil is contraindicated with bexarotene because of increased plasma levels of bexarotene and higher triglyceride levels. In addition, several patients were known to develop pancreatitis in early clinical trials.⁵¹ The preferred lipid-lowering drugs are of the statin or fenofibrate class of agents.⁵² Toxicities associated with systemic retinoids are usually reversible upon cessation of therapy.

Retinoids can be combined with a skin-directed therapy such as PUVA or with other systemic agents including IFN-alpha, ECP, or denileukin diftitox therapy. Combination therapies often have better efficacy and safety profiles when compared to the use of individual biologic agents alone.³

Recombinant Fusion Proteins

Denileukin diftitox is a recombinant cytotoxic fusion protein that targets the IL-2 receptor on T-cells. It is indicated for use in patients with advanced, persistent and recurrent MF and SS.^{53–55} This recombinant fusion protein combines the receptor-binding domain of IL-2 with diphtheria toxin. Once the molecule is bound to the IL-2 receptor, it is taken up by endocytosis, and the diphtheria toxin is cleaved. This leads to inhibition of protein synthesis and results in killing of defined neoplastic cell populations.⁵⁶

Denileukin diftitox is administered intravenously for 5 consecutive days and repeated every three weeks at daily doses of 9 or 18 ug/kg over 1 hour. Toxicities include fever, chills, nausea, a ‘capillary leak’ syndrome, which may be ameliorated by pre- and post-treatment hydration, and a hypersensitivity reaction, which can be countered with premedication with corticosteroids.^{55, 56}

Bexarotene upregulates IL-2 receptors expression on T-cells. Hence, the use of bexarotene may lead to more enhanced binding of denileukin diftitox and greater effectiveness.⁵⁷

Histone Deacetylase Inhibitors

Histone deacetylase inhibitors (HDAC-i) are a novel class of agents. HDAC inhibition results in acetylation of histone and nonhistone proteins leading to a transcriptionally active chromatin and activation of gene expression.⁵⁸ Defective histone-acetylation enzymes have been identified in malignant cells^{59,60}; hence, HDAC-I may have anticancer properties through the restoration of normal acetylation.

There are two HDAC-i used in advanced, refractory, and relapsed MF and SS. The first is vorinostat. It is generally used as monotherapy, but it can be used in combination with other skin directed and systemic agents. However, there is no data for the use of combination therapy involving HDAC-i, and caution is needed with regards

to safety and efficacy. Vorinostat is an oral agent that is dosed orally at 400 mg daily. The most common side effects are gastrointestinal (nausea, vomiting, diarrhea), constitutional, hematologic, and taste disorders.⁶¹ As a result of the gastrointestinal effects, electrolyte abnormalities, particularly in magnesium and potassium, can occur and potentially lead to QT prolongation on EKG. This is more common in patients with a history of heart disease. Other serious side effects to monitor include thromboembolic events, gastrointestinal hemorrhage, ischemic stroke, and thrombocytopenia.⁶¹

A second HDAC-i, romidepsin, is FDA- approved for use in CTCL. It is an intravenous drug used which is primarily used as monotherapy. It is given on days 1, 8, and 15 of a 28-day cycle at a dose of 14 mg/kg/m². Toxicities are similar to those seen in vorinostat.⁶² The same monitoring recommendations are applicable to vorinostat and romidepsin. A clinically meaningful response is seen in up to one-third of patients. In advanced disease, global response rates were higher with romidepsin than vorinostat.^{61,63,64}

MONOCLONAL ANTIBODY THERAPY

One of the most effective monoclonal antibodies used in the treatment of advanced disease such as erythrodermic (T4) MF and SS is alemtuzumab. It is reserved for those patients with advanced disease in whom other traditional therapies have failed. It is a humanized IgG antibody directed against CD52.⁵⁶ CD52 is expressed on T-lymphocytes, B-lymphocytes, natural killer cells, monocyte, and malignant T-cells in CTCL.^{65,66} The mechanism through which alemtuzumab exerts its clinical effect is not well known, but likely includes apoptosis,⁶⁷ antibody-dependent cellular cytotoxicity,^{68,69} and complement mediated cell lysis.^{70,71}

In the standard therapeutic schedule used in other lymphomas, such as chronic lymphocytic leukemia, T-cell prolymphocytic leukemia, and peripheral T-cell lymphoma, escalating doses from 3 to 10 mg and then to 30 mg are administered on alternating days followed by 30 mg three times per week for 12 weeks.⁷²⁻⁷⁵ However, evidence suggests that low dose intermittent alemtuzumab (3 mg on day 1 with 10 mg on days administered subcutaneously thereafter), has equal efficacy and durable remissions with less toxicity.⁷⁶ Alemtuzumab is more efficacious in patients with Sézary syndrome. One of the goals of therapy is to keep the Sézary cell count <1,000 mm³.

Complications of alemtuzumab include serious infections such as cytomegalovirus, generalized herpes simplex virus, fatal, fungal, and mycobacterial infections. Thus, prophylactic regimen of antivirals, antifungals, and antibacterials are typically utilized with alemtuzumab therapy.⁷⁷ In addition, other hematologic toxicities occur, such as severe neutropenia, thrombocytopenia, and anemia.⁷⁷

SYSTEMIC CYTOTOXIC THERAPY (CHEMOTHERAPY)

Systemic chemotherapy is appropriate for patients with large cell transformed stage IIB MF and stage IV MF with extracutaneous involvement. Most chemotherapeutic regimens, however, result in only temporary palliative responses. Multiple single-agent and combination chemotherapies have been tried in advanced MF and SS. For single-agent chemotherapy, no particular drug has been shown to be superior and no large, randomized studies comparing agents have been reported. Single agent chemotherapy is more widely utilized in MF/SS. Combination regimens are largely reserved as salvage after single agent therapy has failed or if there is solid organ involvement.

While typically used in advanced MF and SS, methotrexate has been used in lower doses for extensive stage IB disease (refer to Table 47.6 for I-IIA). Methotrexate inhibits dihydrofolate reductase (DHFR), leading to the subsequent inhibition of DNA synthesis.⁷⁸ Multiple dose ranges and schedules have been used as therapy in erythrodermic MF (T4) and SS. No clear benefit has been demonstrated for higher doses compared to lower doses of methotrexate. Side effects observed with the use of methotrexate include elevated serum aminotransferase levels (which are usually reversible after dose reduction or withdrawal), oral mucositis, pharyngeal mucositis, gastrointestinal complications such as nausea and diarrhea, interstitial pulmonary fibrosis, and uncommonly, reversible leucopenia.⁷⁹

Gemcitabine, a novel nucleoside analog, is activated by deoxycytidine kinase to its triphosphate form, gemcitabine triphosphate, which is then incorporated into RNA and DNA. The latter causes chain termination and inhibition of DNA repair, which is responsible for antitumor effect of the medication. Response rates as high as 70% have been reported, but the complete remission rate is low with a median duration of complete remission of 10 months (range 4-22 months).⁸⁰ Recently this agent has been used as front-line therapy for patients in whom control is needed of massive lymph node disease (see Table 47.15). Gemcitabine is generally well tolerated, even in the elderly population. Myelosuppression with resulting anemia, thrombocytopenia, or leukopenia are the most common adverse events.⁸⁰ Cutaneous adverse events include flares of lesional erythema within 1 week of treatment, as well as generalized hyperpigmentation.⁸⁰ Serious adverse events are rare.

Doxorubicin is an anthracycline agent used in advanced stages of MF and SS. Pegylated liposomal doxorubicin is a formulation of doxorubicin that is encapsulated into liposomes. The liposomes serve as stable, long-circulating carriers useful for delivering doxorubicin to tumor sites with a lower toxicity than the free drug. The most frequent side effects are mild anemia and lymphopenia. Another significant toxicity with this class of drugs is palmoplantar erythrodysthesia.⁸¹

A new cytotoxic agent is temozolomide, which has shown encouraging activity in advanced MF. It is an imidazotetrazine derivative and oral alkylating agent that has excellent oral bioavailability.⁸² Its mechanism of action is similar to that of other alkylating agents, which induce DNA damage by cross-linking. Resistance has been associated with high levels of the scavenger protein O6-alkylguanine-DNA alkyltransferase in tumor cells. Response rates of 30% have been reported in stage IIB and III patients. In a phase II study, the most frequent adverse effects were nausea, vomiting, neutropenia, and thrombocytopenia.⁸²

In addition, other mechanisms to inhibit growth and encourage apoptosis of tumor cells are being developed. Bortezomib, which inhibits the proteasome, leads to the down-regulation of NF-KB activation and induction of CTCL cell apoptosis.⁸³ In a phase II trial, the response rate was 67% in all stages; however, the complete response rate was much lower at 10%.⁸⁴ With regard to hematologic adverse effects, neutropenia and thrombocytopenia were observed. The most significant nonhematologic toxicity was sensory neuropathy.⁸⁴

The purine analogs are a class of drugs that have demonstrated activity in MF and a variety of other non-Hodgkin lymphomas. T-cells have a high level of adenosine deaminase (ADA), a key enzyme in the purine degradation pathway. The purine analogs pentostatin, fludarabine, and 2-chloro-deoxyadenosine are a group of structurally similar agents, which were developed to target ADA. They have different interactions with ADA, but all result in DNA damage. Hematologic toxicity and opportunistic infections are the most common complications associated with this class of drugs. Prophylactic antibiotics against *Pneumocystis carinii* and antivirals to prevent herpes virus infection are routinely indicated.⁸⁵

Most of the patients treated with combination chemotherapy have failed single agent chemotherapy or have solid organ involvement (IIB to IV). There are no randomized trials comparing combination chemotherapy to single-agent regimens. The largest experience is with combinations such as cyclophosphamide, vincristine, and prednisone, with or without doxorubicin.^{86,87} Complete response rates are generally about 25% (range 11-57%) and response duration is 3-20 months.

HEMATOPOIETIC STEM CELL TRANSPLANTATION

There has been recent interest in using hematopoietic stem cell transplantation in MF. Given the small number of patients treated thus far, there are no well-defined prognostic factors to identify patients suitable for this therapy.

Bigler and associates reported that five of six patients achieved a complete response with an autologous

transplant.⁸⁸ In another study, eight of nine patients achieved a complete response.⁸⁹ However, all of the patients in these studies ultimately relapsed, suggesting that autologous transplantation is not a curative approach.

The concept of allogeneic hematopoietic stem cell transplantation (HSCT) is promising. Even in the absence of a complete response, an allogeneic graft-versus-tumor effect may provide an immune mechanism to control the malignant T-cell process associated with mycosis fungoides. Molina and associates reported a complete response in all eight patients transplanted for refractory MF or SS. With a median follow-up of 56 months, six patients remained alive and without evidence of lymphoma.⁹⁰ Mild acute and chronic GVHD developed in all patients who survived. A non-myeloablative approach has also been reported in which all three patients who achieved a durable complete response.⁹¹

It appears that compared to autologous HSCT, allogeneic HSCT may result in durable long-term remissions.⁹² With better understanding of the disease biology, it may be possible to develop prognostic factors so that these aggressive approaches can be offered to suitable patients. Larger studies will be required to identify the best conditioning regimen, efficacy, safety, and impact on quality of life.

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Treatment of Kaposi's Sarcoma

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INTRODUCTION

Kaposi's sarcoma (KS) was originally described in 1872 by Moritz Kaposi, a Hungarian dermatologist, as multifocal pigmented sarcoma of the skin in five European men.¹ KS has since been categorized into four types, including classic, endemic, iatrogenic immunosuppression-associated, and epidemic, or AIDS-associated, KS. Kaposi's sarcoma-associated herpesvirus (KSHV), or human herpesvirus 8 (HHV8), is a primary factor for the development of all types of KS and the histologic features are indistinguishable; however, the clinical variants have a distinct epidemiology and clinical course.

EPIDEMIOLOGY AND CLINICAL PRESENTATIONS

Classic, or Mediterranean KS, occurs primarily in elderly men of Mediterranean or Eastern European descent. Classic KS typically presents as slowly progressing violaceous to red-brown nodules or plaques that begin on the hands and feet and progress to more widespread involvement over years. Lymphedema may be present and visceral or mucosal involvement develops in approximately 10% of patients.² Endemic African KS occurs in non-HIV-infected patients in Africa and has a variety of clinical manifestations, including slow-growing nodular cutaneous disease in young adults, aggressive invasive localized cutaneous disease, florid mucocutaneous and visceral disease, and fulminant lymphadenopathic disease that rapidly progresses and most often occurs in young children.³

The incidence of KS rose dramatically with the HIV epidemic. Epidemic, or AIDS-associated, KS occurs more commonly with decreasing CD4 counts and has a variety of clinical manifestations, ranging from localized or diffuse cutaneous disease (Figure 48-1) to aggressive and rapidly progressive oral, mucocutaneous, or visceral disease. Mucocutaneous lesions may appear as violaceous to hyperpigmented patches, papules, plaques, nodules, or tumors and may be associated with lymphedema (Figure 48-2) or lymphadenopathy. HIV-infected patients with KS tend to have a better prognosis if they have lesions confined to the



FIGURE 48-1 Diffuse cutaneous Kaposi's sarcoma manifesting as numerous violaceous plaques and nodules.



FIGURE 48-2 Violaceous plaques of Kaposi's sarcoma on the face with associated lymphedema.

skin, minimal to no oral involvement, a CD4 count above $200 \times 10^6/L$, no opportunistic infections, and no fever or weight loss.⁴

Iatrogenic immunosuppression-associated KS most commonly occurs in organ transplant patients who are receiving chronic immunosuppressive medications. The median time to develop KS post-transplant in one study ranged from 4 to 108 months (median 10 months), and there was a predominance of patients with Italian ancestry.⁵ Clinical presentation ranges from localized or diffuse

cutaneous disease to aggressive visceral involvement. Resolution or improvement of disease with a decrease in immunosuppression may occur.

ETIOLOGY/DIAGNOSIS

Kaposi's sarcoma-associated herpesvirus, or HHV8, is a primary factor for the development of all types of KS. Serologic studies have shown that infection rates with HHV8 parallel the incidence of KS, with low rates in the United States, intermediate rates in the Mediterranean countries, and the highest rates in Central Africa.² The acquisition of the HHV8 virus varies, with sexual transmission predominating in the developed world and early non-sexual childhood acquisition or mother-to-child transmission being most common in African countries.⁶ The diagnosis is most reliably made with histologic examination of tissue, and the findings are indistinguishable, regardless of the clinical type of disease. Histologic features include a dermal proliferation of spindle cells with numerous slit-like vascular spaces. Extravasated erythrocytes, hemosiderin-laden macrophages, and inflammation with plasma cells are often present. Immunohistochemical staining for HHV8 will highlight lesional nuclei.

GOALS OF TREATMENT

The treatment of epidemic, or AIDS-related, Kaposi's sarcoma will be the focus of this systematic review. Curative therapy is not currently available for AIDS-related KS; however, palliative therapy can be beneficial in many ways. Treatment can improve the cosmetic appearance of lesions, symptomatically improve painful or edematous lesions, and relieve symptoms caused by oral or visceral involvement. Limited disease is best treated with local therapy, while diffuse or disseminated disease may require systemic therapy.⁷

The clinical trials discussed below uniformly use (unless otherwise indicated) the AIDS Clinical Trials Group Oncology Committee criteria for evaluating KS and its response to treatment. These clinical response criteria have been standardized and include: complete response (absence of residual KS for at least 4 weeks), partial response ($\geq 50\%$ reduction in size or at least 50% flattening of the lesions), stable disease (not fulfilling the criteria for partial or progressive disease), and progressive disease ($\geq 25\%$ increase in size or change of macular lesion to papular, nodular or plaque-like).⁸

SEARCH METHODOLOGY

Randomized controlled trials of all therapy for AIDS-related Kaposi's sarcoma were included in the search. The Cochrane Library for systematic reviews (2009) and Pubmed/Medline (1966–September 2009) were searched.

QUESTION

In patients with localized AIDS-related KS, what is the efficacy, defined as a complete or partial response, of local therapies, including topical medications, intralesional injections, radiotherapy, or surgical interventions? (Table 48-1)

LOCAL THERAPY

Local therapy is helpful for treatment of cosmetically undesirable lesions or localized symptomatic disease; however, it is not useful for disseminated disease or in the prevention of the development of new lesions. Several localized therapies have been reported to be successful but have not been proven in randomized controlled trials, and these include surgical excision, laser therapy, cryotherapy, topical immunotherapy with imiquimod, and photodynamic light therapy.

INTRALESIONAL THERAPY

Efficacy

Patients with AIDS-related KS were evaluated for the efficacy and pain associated with intralesional vinblastine with or without 1% bicarbonate-buffered lidocaine (BBL). Eleven patients were enrolled and six untreated KS lesions in a similar anatomic location were selected on each patient. These lesions were randomly assigned to one of six groups: vinblastine, vinblastine mixed with BBL, vinblastine 5 minutes after BBL injection, or one of three control groups, which included BBL, saline, or no treatment. The vinblastine groups showed a complete response in 20 (61%) lesions and a complete or partial response in 29 (88%) lesions total. There was no significant difference in efficacy among the vinblastine groups. Pretreatment with BBL reduced the pain from vincristine injection significantly.⁹

Another double-blind randomized trial enrolled 16 patients and compared the clinical efficacy of intralesional vinblastine and 3% sodium tetradecyl sulfate (STS) in the treatment of oral Kaposi's sarcoma (OKS). STS is an agent that can cause fibrotic obliteration of the tumor through ischemic necrosis. The patients received one intralesional injection after local anesthesia. Mean tumor reduction size was similar in both groups, with 0.68 cm reduction in the vinblastine group and 0.61 cm reduction in the STS group. Complete or partial response was achieved in two vinblastine patients, and four STS patients had partial responses.⁷

Drawbacks

Although pretreatment with BBL in the first study reduced the vincristine injection pain, many patients reported an

TABLE 48-1—Summary of Randomized Controlled Trials of Localized Treatment for AIDS-Related KS

First author, Reference	Regimen	Study population	Sample size	Duration of treatment	Results
Boudreax (1993) ⁹	Intralesional vinblastine with or without 1% bicarbonate-buffered lidocaine vs. placebo	HIV-infected patients >18 years old with untreated cutaneous KS lesions	11	Single intralesional injection	Vinblastine groups showed a CR in 20 (61%) lesions and a CR or PR in 29 (88%) lesions total. Placebo groups showed a CR or PR in 5 (15%) lesions total. ($p<0.001$)
Ramírez-Amador (2002) ⁷	Intralesional vinblastine vs. intralesional 3% sodium tetradecyl sulfate (STS)	HIV-infected patients >18 years old, with nodular KS on the hard palate	16	Single intralesional injection	Mean tumor reduction size was similar in both groups, with 0.68 cm reduction in the vinblastine group and 0.61 cm reduction in the STS group. ($p=0.80$) CR or PR was achieved in two vinblastine patients, and four STS patients had PR. ($p=0.61$)
Bodsworth (2001) ¹⁰	Alitretinoin gel or vehicle gel twice daily	HIV-infected patients >18 years old with cutaneous KS	134	12 weeks	The overall patient response rate (CR + PR) was 37% (23 of 62) for the alitretinoin-treated patients and 7% (5 of 72) for the vehicle-treated patients. ($p=0.00003$)
Stelzer (1993) ¹¹	Radiotherapy: 8 Gy in 1 fraction vs. 20 Gy in 10 fractions vs. 40 Gy in 20 fractions.	HIV-infected patients >18 years old with cutaneous KS	14	5 times per week until completed fractions	CR was significantly higher with 40 Gy (83%) and 20 Gy (79%) than with 8 Gy (50%). ($p=0.04$)
Singh (2008) ¹²	Radiotherapy: 24 Gy in 12 fractions vs. 20 Gy in 5 fractions	HIV-infected patients >18 years old with cutaneous or mucosal KS	50	5 times per week until completed fractions	The overall patient response rate (CR + PR) was similar with 24 Gy (21/23) and 20 Gy (26/27) regimens. ($p=0.73$)

CR, complete response; PR, partial response

aching pain for 6-48 hours after the injection that could deter from additional intralesional treatment. Nearly all of the lesions that responded healed with hyperpigmentation, which may not be cosmetically desirable to some patients. Several of the enrolled patients were seen 4-7 months after treatment, and 5 of the 12 (42%) evaluated lesions that had completed responded originally had relapsed.⁹

In the second study, mouth pain and oral ulcers were common patient complaints with both agents during the first week after treatment.⁷

Comment

Intralesional therapy, such as vinblastine, may provide complete or partial improvement of localized cutaneous or oral AIDS-related KS. This may be particularly useful in patients that have few lesions, as this method may not be feasible for extensive disease. In addition, this may be a good treatment option for patients that have localized symptomatic or cosmetically undesirable lesions and are not candidates for systemic therapy.

TOPICAL RETINOID

Efficacy

After 12 weeks of twice daily topical application, the overall patient response rate (complete plus partial response) to the selected lesions of cutaneous Kaposi's sarcoma was 37% (23 of 62) for the alitretinoin-treated patients and 7% (5 of 72) for the vehicle-treated patients ($p=0.00003$). Lesions qualified for partial response if there was approximately 50% measured improvement, and complete improvement indicated the lesion was completely cleared except for pigmentation from residual hemosiderin.¹⁰

Drawbacks

Almost half (49%) of the patients reported a rash, which was further described as erythema, scaling, irritation, redness, rash, or dermatitis. Four patients (3%) withdrew from the study because of an adverse event attributed to study medication and all were considered cases of grade three dermal irritation.¹⁰

Among patients receiving alitretinoin gel, the median time to onset of response was 29 days, and this delay in improvement, as well as the continued need for treatment, could contribute to a lack of compliance in the beginning of treatment.¹⁰

Comment

In this study, 10 patients (16%) in the treatment group had both cutaneous and visceral disease, and 22 patients (36%) had received previous systemic therapy. Eight of these patients were considered either unresponsive (i.e., failed to achieve $\geq 50\%$ improvement) to at least one such treatment or wholly refractory (failed to achieve at least a partial response to all prior systemic therapies).¹⁰ The use of this treatment would be considered palliative in patients with extensive cutaneous and visceral disease.

RADIOTHERAPY

Efficacy

Fourteen patients were randomized to receive one of three radiation-dosing regimens: 8 Gy in one fraction, 20 Gy in 10 fractions, or 40 Gy in 20 fractions. Complete response (complete resolution of palpable tumor) was significantly higher with 40 Gy (83%) and 20 Gy (79%) than with 8 Gy (50%) ($p=0.04$). Median time to treatment failure (any measurable tumor growth) was 43 weeks with 40 Gy, 26 weeks with 20 Gy, and 13 weeks with 8 Gy ($p=0.003$). This study showed that fractionated radiotherapy with higher total doses resulted in improved response and control of cutaneous Kaposi's sarcoma.¹¹

Given the findings that fractionated radiotherapy with higher total doses was shown to be effective, another study was designed to determine whether a hypofractionated regimen of radiotherapy would be beneficial. Sixty patients were randomly assigned to receive the standard regimen at the study hospital (24 Gy in 12 fractions) to one arm and a shorter-duration regimen of 20 Gy in five fractions to the other arm. The difference in complete and partial response rates, as well as the median local recurrence-free survival, was similar between the two groups.¹²

Drawbacks

The incidence of acute and late radiation skin toxicity was increased in higher-dose groups; however, the side effects were limited to erythema, dry desquamation, alopecia, and hyperpigmentation.¹¹ None of the side effects required disruption of therapy. In addition, the fractions of radiation were given daily, 5 days per week. This can be a rigorous treatment schedule for many patients. In the lesions that respond to treatment, median time to treatment failure ranged from 13 to 43 weeks, and lesions may need to be retreated.^{11,12}

The first study described above only treated cutaneous lesions in a limited electron field.¹¹ Treatment of KS-related edema or disseminated cutaneous involvement may require extensive radiotherapy fields, which was beyond this study, and the clinical response and side effects may be very different.

Comment

The role of radiation therapy in AIDS-related KS is either cosmetic treatment of localized cutaneous disease or palliative therapy for painful and/or edematous lesions. If radiotherapy is chosen as a treatment for one of these reasons, the individual situation will dictate the therapeutic regimen. Fractionated radiotherapy with higher total doses will likely give greater cosmetic results, and patients may choose a regimen that requires numerous treatments with a better chance of success. On the other hand, a debilitated and bed-ridden patient with painful edematous lesions may choose a regimen, such as 8 Gy in one fraction, that may provide symptomatic relief with few visits.

QUESTION

In patients with severe or disseminated AIDS-related KS, what is the efficacy, defined as a complete or partial response, of systemic therapies? (Table 48-2)

SYSTEMIC THERAPY

The decision to initiate systemic therapy is based on multiple factors, including the extent of Kaposi's sarcoma, visceral involvement, and degree of immunosuppression.¹³ Prognostic factors for AIDS-related KS have also been determined in order to allow clinicians to make an accurate assessment of the patient and guide therapeutic decisions. Factors that are associated with a poorer prognosis include an age of 50 years or older and having another concurrent AIDS-associated illness. An improved prognosis is associated with having KS as the AIDS-defining illness and a higher CD4 count.¹⁴

CHEMOTHERAPY

Cytotoxic Chemotherapy

Before the development of liposomal anthracyclines and highly active antiretroviral therapy (HAART), cytotoxic chemotherapy regimens were the treatment of choice for disseminated and/or severe AIDS-related KS. These regimens included vinblastine alone, etoposide alone, vincristine alone, dual therapy with vinblastine and another chemotherapeutic agent, or a combination of doxorubicin, bleomycin, and vinblastine (ABV). ABV was found to be more effective than single-drug regimens in randomized trial that treated patients with severe AIDS-related KS.¹⁵

TABLE 48-2—Summary of Randomized Controlled Trials of Systemic Chemotherapy for AIDS-Related Kaposi Sarcoma

First author, Reference	Regimen	Study population	Sample size	Duration of treatment	Results
Gill (1996) ¹⁶	Liposomal daunorubicin vs. doxorubicin, bleomycin, and vincristine (ABV)	HIV-infected patients >18 years old with advanced KS, defined as ≥ 25 mucocutaneous lesions, symptomatic visceral involvement, or tumor-associated lymphedema.	232	Every 2 weeks until CR, disease progression, or unacceptable toxicity.	The overall response rate (CR + PR) was 25% (3 CRs and 26 PRs) for liposomal daunorubicin and 28% (one CR and 30 PRs) for ABV. (95% confidence interval, – 14% to +9%).
Stewart (1998) ¹⁸	Pegylated liposomal doxorubicin or bleomycin and vincristine (BV) combination	HIV-infected patients >18 years old with either ≥ 15 mucocutaneous lesions (and developed more than 5 cutaneous lesions in preceding month) OR with documented visceral KS with at least five assessable cutaneous lesions.	121	Every 3 weeks with a maximum of six cycles.	The overall response rate (CR + PR) was 58.7% for the patients treated with pegylated liposomal doxorubicin compared to 23.3% treated with BV ($p < .001$).
Northfelt (1998) ¹⁹	Liposomal doxorubicin vs. ABV combination.	HIV-infected patients >18 years old with progressive biopsy-proven AIDS-KS with ≥ 25 mucocutaneous lesions or the development of 10 or more new lesions in the preceding month, or documented visceral disease.	258	Every 14 days to a maximum of six cycles.	The overall response rate (CR + PR) was 45.9% for the patients treated with pegylated liposomal doxorubicin compared to 24.8% treated with ABV ($p < .001$).
Cooley (2007) ²⁰	Pegylated liposomal doxorubicin vs. liposomal daunorubicin	HIV-infected patients >18 years old with AIDS-related KS requiring systemic chemotherapy, a life expectancy of at least 120 days, and at least 5 measurable mucocutaneous KS lesions.	80	Every 2 weeks with a maximum of six cycles.	Overall tumor responses (CR + PR) were observed in 55.0% (33/60) of pegylated liposomal doxorubicin patients (compared to 31.6% (6/19) of liposomal daunorubicin patients).
Martin-Carbonero (2004) ²³	HAART regimen plus pegylated liposomal doxorubicin or HAART regimen alone.	HIV-infected patients >18 years old, either naive or failing HAART with moderate–advanced KS (at least 10 cutaneous lesions or mucosal or visceral involvement).	28	Liposomal doxorubicin was given every 3 weeks	After 48 weeks of follow-up, response rates (CR + PR) in the HAART plus pegylated liposomal doxorubicin group were 76%, as compared to 20% in the group treated with HAART alone. ($p=0.003$)

CR, complete response, PR, partial response, HAART, highly active antiretroviral therapy.

ABV was a commonly used multi-drug chemotherapeutic regimen for severe AIDS-related Kaposi's sarcoma until the development of liposomal anthracyclines.

LIPOSOMAL DAUNORUBICIN

Background

At the time of the study, cytotoxic chemotherapy, including the regimen of doxorubicin, bleomycin, and vincristine (ABV), was the most successful treatment modality for KS, especially for advanced disease with visceral involvement and patients with severe immunosuppression. This liposomal anthracycline formulation demonstrated a significantly better pharmacokinetic and side-effect profile than conventional daunorubicin in preliminary studies, and

this study compared liposomal daunorubicin to ABV in the treatment of advanced AIDS-related KS. Patients were randomized to receive one of the regimens every 2 weeks, and treatment was continued until complete response, disease progression, or unacceptable toxicity.¹⁶

Efficacy

The overall response rate (complete or partial response) was 25% for liposomal daunorubicin and 28% for ABV, which was not a statistically significant difference. The median survival time for the two groups (369 days for liposomal daunorubicin and 342 days for ABV) and median time to treatment failure (115 days for liposomal daunorubicin and 99 days for ABV) was similar and not significantly different between the groups. ABV patients had significantly

more alopecia and neuropathy, but the patients treated with liposomal daunorubicin experienced more severe neutropenia.¹⁶

Drawbacks

ABV patients had significantly more alopecia and neuropathy, but the patients treated with liposomal daunorubicin experienced more severe neutropenia.¹⁶

Comment

This study was done before the wide availability of HAART and was the first randomized comparison of a liposomal anthracycline medication to standard cytotoxic chemotherapy. Although the efficacy was similar in the two groups, several nonhematologic side effects were significantly decreased in the group treated with liposomal daunorubicin.¹⁶ Overall, liposomal daunorubicin was shown to be a promising alternative to the traditional chemotherapy regimens.

PEGYLATED LIPOSOMAL DOXORUBICIN

Background

At the time of the study, cytotoxic chemotherapy, including the regimens of doxorubicin, bleomycin, and vincristine (ABV), as well as bleomycin and vincristine (BV), were still the treatment of choice for advanced AIDS-related KS. The pegylated liposomal form of doxorubicin had been shown in preliminary studies to have a significantly longer plasma half-life and more targeted delivery of the medication.¹⁷ Two randomized studies compared clinical response and toxicity of pegylated liposomal doxorubicin to traditional chemotherapy, including BV and ABV.^{18,19}

Efficacy

The first study randomly assigned 121 patients to receive pegylated liposomal doxorubicin or the BV combination. Complete or partial responses were achieved in 58.7% of the patients treated with pegylated liposomal doxorubicin compared to 23.3% treated with BV ($p < .001$). Thirty-two (26.7%) of the patients who received BV withdrew from the study prematurely because of a chemotherapy-related adverse events, compared to 13 (10.7%) who received pegylated liposomal doxorubicin. The significant side effects were different for the two groups, with paresthesia and peripheral neuropathy significantly higher in patients who received BV, whereas leukopenia and oral candidiasis were more commonly seen in patients treated with pegylated liposomal doxorubicin.¹⁸

The second study randomly assigned 258 patients to receive pegylated liposomal doxorubicin or the ABV

combination. Complete or partial responses were achieved in 45.9% of the patients treated with pegylated liposomal doxorubicin compared to 24.8% treated with ABV ($p < .001$). In addition, disease progression was seen in two (1.5%) of the patients treated with pegylated liposomal doxorubicin, compared to 10 (8.0%) treated with ABV ($p < .001$). Significantly more patients treated with ABV discontinued treatment because of an adverse event (37%) compared to 11% treated with pegylated liposomal doxorubicin. Nausea and vomiting, alopecia, and peripheral neuropathy were significantly more common in patients treated with ABV. The most common adverse event in both groups was leukopenia, and there was no significant difference between the two groups.¹⁹

Drawbacks

Leukopenia is the most significant adverse event with pegylated liposomal doxorubicin treatment; however, granulocyte colony-stimulating factors can limit this side effect. Several acute infusion-related reactions occurred in the pegylated liposomal doxorubicin group, but most of these occurred with the initial infusion. Pretreatment with antihistamines and/or corticosteroids allowed for the continuation with subsequent infusions.¹⁹

Comment

These studies confirmed that pegylated liposomal doxorubicin was more effective in the treatment of severe AIDS-related KS than standard cytotoxic therapeutic regimens. The side effect profile and tolerance of pegylated liposomal doxorubicin is, over all, manageable and improved over standard chemotherapy, and liposomal anthracyclines are now considered first-line therapy.

PEGYLATED LIPOSOMAL DOXORUBICIN COMPARED TO LIPOSOMAL DAUNORUBICIN

Background

Both pegylated liposomal doxorubicin and liposomal daunorubicin are now approved treatments for AIDS-related Kaposi's sarcoma. Liposomal anthracyclines are considered first-line therapy in patients with widely disseminated KS, and the pegylated form of liposomal doxorubicin is thought to more effectively distribute the drug to tumors that have abnormal vasculature. This study evaluated the clinical benefit, tumor response, and tolerance of pegylated liposomal doxorubicin and compared it to liposomal daunorubicin. Clinical benefit was defined as improvement from baseline in at least one of five AIDS-related KS symptom categories that lasted for more than 4 weeks, in the absence of disease progression or severe

drug-induced toxicity. These symptom categories include functional impairment from KS-associated edema, symptomatic and evaluable pulmonary KS, symptomatic and evaluable gastrointestinal KS, moderate or severe KS-associated pain despite analgesic use, and KS lesions that are disfiguring and impairing. Tumor response was evaluated by comparing lesion characteristics, such as size, number, appearance, and sites of involvement.²⁰

Efficacy

Clinical benefit was achieved in 48 out of 60 (80.0%) patients receiving pegylated liposomal doxorubicin for a median duration of 62 days. Of the patients receiving liposomal daunorubicin, 12 of 19 (63.2%) achieved clinical benefit that lasted for a median duration of 55 days. Tumor responses (at least partial responses) were observed in 55.0% (33 out of 60) of pegylated liposomal doxorubicin patients (compared to 31.6% [6 out of 19] of liposomal daunorubicin patients), with a median time to tumor response similar in each group.²⁰

Drawbacks

Dose adjustments, primarily caused by hematologic toxicity, were required in 68.3% of patients receiving pegylated liposomal doxorubicin and 63.2% of patients receiving liposomal daunorubicin. Six (7.7%) doses were interrupted because of infusion-related reactions in pegylated liposomal doxorubicin patients; however, there were no dose interruptions in the liposomal daunorubicin group.²⁰

Comment

This randomized comparative trial shows that pegylated liposomal doxorubicin is a safe and effective therapy for AIDS-related Kaposi's sarcoma and has an improved clinical benefit and tumor response when compared to liposomal daunorubicin. Although the side-effect profile is similar for these medications, dose adjustments secondary to hematologic toxicity (most commonly neutropenia) were twice as common with the pegylated liposomal doxorubicin.²⁰ Over all, the liposomal formulations of both medications have allowed for a decrease in hematologic side effects and cardiotoxicity.

HIGHLY ACTIVE ANTIRETROVIRAL THERAPY (HAART) WITH OR WITHOUT SYSTEMIC CHEMOTHERAPY

Background

Although the prevalence of KS has significantly decreased with the advent of HAART, KS and non-Hodgkin's lymphoma are still the most common causes of death from AIDS-related malignancies, accounting for a combined

total of over 40% of all malignancy-related deaths in HIV-infected patients.^{21,22} This randomized study evaluated the treatment of HIV patients with moderate to advanced KS who were either naive or failing HAART. The patients were treated with either a new HAART regimen plus pegylated liposomal doxorubicin or a new HAART regimen alone.²³

Efficacy

After 48 weeks of follow-up, response rates were clearly different between the two groups. The response rates in the HAART plus pegylated liposomal doxorubicin group were 76%, as compared to 20% in the group treated with HAART alone. These findings suggest that HAART may not be enough for adequate KS treatment in patients with moderate to advanced disease.²³

Drawbacks

In some geographical areas of the world with a particularly high incidence of AIDS-related KS, systemic chemotherapy regimens may not be available. If HAART alone is a choice of treatment, patients may still experience significant improvement of disease with this regimen.

The HAART plus pegylated liposomal doxorubicin group experienced more side effects, with an adverse event being reported in one-third of patients. The most common side effects included anemia and neutropenia.²³

Comment

This was the first randomized study to assess the direct effect of HAART on HIV-related KS regression. Several other smaller studies and anecdotal reports have shown more cases of KS regression with HAART alone; however, these were not randomized trials, many included patients with mild disease, and often patients were receiving concomitant local or systemic therapy. Although HAART may provide a decrease in the burden of disease from KS, patients who do not significantly respond to HAART alone or who have moderate to severe KS may benefit from the addition of systemic chemotherapy, such as pegylated liposomal doxorubicin.²³

OTHER SYSTEMIC THERAPY

Many systemic treatments have been considered for the treatment of AIDS-related KS, but few have been evaluated in randomized controlled trials. Many of these have been evaluated for safety and efficacy in phase II, but not phase III, trials. However, some of them are approved for treatment of KS and deserve brief mention.

Taxanes are a class of chemotherapy drug that inhibit angiogenesis and have found to be effective in AIDS-related KS. Paclitaxel is approved for treatment of KS in

the United States and has shown significant efficacy in two phase II trials, even in patients with advanced disease and KS found to be resistant to liposomal anthracyclines.^{24,25} Potentially life-threatening drug-drug interactions have been reported between paclitaxel and some HAART regimens, and dose modifications and close monitoring may be necessary.²⁶ Docetaxel is another taxane that has shown promise in treating advanced AIDS-related KS in small studies.²⁷

Other systemic therapies that have shown efficacy in phase II or small studies include interferon alpha, matrix metalloproteinases (MMP), and interleukin 12.¹³

ANGIOGENESIS INHIBITORS

Background

Angiogenesis plays a role in the development of KS lesions and has therefore become a target of therapy. IM862 is a synthetic dipeptide (*L*-glutamine *L*-tryptophan) that has no direct cytotoxic effects, but exhibits dose-dependent inhibition of angiogenesis. Other inhibitors of angiogenesis, such as thalidomide and VEGF receptor inhibitors, have been considered, but IM862 is the only one that underwent a randomized controlled trial for the treatment of AIDS-related KS.²⁸

Efficacy

Two hundred and two patients with AIDS-related KS were randomly assigned to receive 5 mg intranasally every other day of the medication or placebo. There were no complete remissions and the partial response rate was similar in both treatment arms (IM862, 23%; placebo, 21%).²⁸

What We Know

- Curative therapy is not currently available for AIDS-related KS; however, palliative therapy can be beneficial in many ways.
- Local therapy is helpful for treatment of cosmetically undesirable lesions or localized symptomatic disease; however, it is not useful for disseminated disease or in the prevention of the development of new lesions.
- Many local therapies that are used in clinical practice, including surgical excision, laser therapy, cryotherapy, topical immunotherapy, and photodynamic light therapy, have not been evaluated with proper clinical trials.
- Local therapies that have shown efficacy in randomized controlled trials in treatment of limited KS include intralesional vinblastine, radiotherapy, and topical alitretinoin.

Drawbacks

In order to qualify for the study, patients needed at least five or more measurable lesions of biopsy-proven AIDS-related KS involving the skin or the oral cavity. Patients with symptomatic visceral disease or who required chemotherapy were excluded, and this is an important group in which to investigate this medication as a primary or adjunct treatment for KS.²⁸

Comment

At the dose and schedule used in this study, IM862 was no better than placebo in treating AIDS-related KS. In addition, time to progression of disease was statistically significantly shorter in the patients taking IM862 compared to placebo, which may suggest that IM862 actually accelerates progression of KS.²⁸ More investigation of the use of angiogenesis inhibitors is needed in order to assess their potential use in AIDS-related KS.

HHV8 SUPPRESSION

Background

HHV8 is an essential factor in the development of AIDS-related KS. Because there is preliminary evidence that ganciclovir may have an antiviral effect against HHV8, it was hypothesized that valganciclovir would reduce HHV8 replication *in vivo*. Sixteen HIV-positive and 10 HIV-negative men who were observed in previous trials to shed HHV8 from the oropharynx were enrolled to receive either valganciclovir, 900 mg once daily, or placebo, for 8 weeks, and daily oropharyngeal swabs were taken.²⁹

- The decision to initiate systemic therapy is based on multiple factors, including the extent of Kaposi's sarcoma, visceral involvement, and degree of immunosuppression.
- Liposomal anthracyclines have been shown to be effective in the treatment of severe AIDS-related KS in randomized controlled trials and are currently first-line systemic therapies.
- Many other systemic agents, such as the taxanes, have been developed and show promise in the treatment of advanced KS; however, no randomized controlled trials have been conducted using these medications in AIDS-related KS.
- HAART therapy alone may not be sufficient in the treatment of moderate to severe AIDS-related KS, and systemic chemotherapy may need to be added for optimal response.

Efficacy

HHV-8 was detected on oropharyngeal swabs 44% of the enrolled days for the placebo group versus 23% in the valganciclovir group ($p=0.02$). HHV8 replication returned when the valganciclovir was discontinued, which indicated the need to use daily dosing for effective virologic control.

Drawbacks

Patients taking valganciclovir more frequently reported diarrhea, but no serious adverse events were observed during the study.

Comment

Although this study indicated that valganciclovir reduces HHV8 replication in the oral mucosa, more studies will need to be done in order to assess whether this correlates with prevention or suppression of AIDS-related KS.

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Treatment of Chronic Wounds

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INTRODUCTION AND SEARCH METHODOLOGIES

Chronic wounds cause significant morbidity and are a major health care burden affecting 6.5 million patients annually in the United States.¹ Almost \$25 billion per year is spent on the treatment of chronic wounds, which represents greater than 50% of all skin care expenditures in the United States.² The cost of treating chronic wounds will continue to increase rapidly because of growing health care costs, an aging population, and a sharp rise in the incidence of diabetes and obesity. Chronic wounds are often disguised as a comorbid condition associated with highly branded diseases such as diabetes. As a result, the true impact of chronic wounds on public health and the economy is often unrecognized. Furthermore, chronic wounds are treated by a wide variety of health care professionals, and less frequently by dermatologists. At present, over 1000 outpatient wound centers are in operation in the United States, which does not include wound care rendered in physician's offices, inpatient acute care hospitals, long-term facilities, and nursing homes.¹ Given the tremendous and still increasing burden of chronic wounds, dermatologists should endeavor to take greater responsibility for the management of patients with chronic wounds. In addition, wound research is a rapidly developing scientific field. Dermatologists have the opportunity to contribute to rigorous basic science, skin biology, translational and clinical investigation in this growing arena.

A chronic wound has failed to proceed through the orderly and timely process of repair.³ By definition, it is an ulcer, which does not show signs of progress after 6 weeks or manifests frequent recurrences.⁴ Chronic wounds rarely affect healthy people. Most patients suffer from comorbidities that predispose them to delayed healing. These conditions include venous insufficiency, diabetes, physical immobility, arterial disease and a myriad of dermatologic conditions such as vasculitis and pyoderma gangrenosum. In addition, poor nutrition, obesity, and wound infection play a major role in impeding the healing process. This chapter will introduce recent epidemiologic data and common etiologies related to chronic wounds. Discussion will focus on principles of wound care, current treatment modalities, and the role of wound microbiology. Up-to-date

evidence has been collected by repeated searches using PubMed, Scopus, and the Cochrane Library for frequently cited publications, articles in high impact journals, comprehensive reviews, and randomized clinical trials. The information is supplemented by the authors' firsthand clinical experience and knowledge of the subject.

ETIOLOGIES OF THE CHRONIC WOUND

Venous insufficiency is responsible for at least 75% of lower extremity ulcerations.⁵ Venous leg ulcers are the most severe manifestation of chronic venous incompetence, producing venous hypertension and turbulent flow related to reflux through incompetent valves in the lower extremities. Approximately 80% of the adult population have some degree of venous disease, manifested by telangiectases, varicose veins, edema, stasis dermatitis, lipodermatosclerosis and ulcerations.⁵ Risk factors such as obesity, prolonged standing, and genetic predisposition can increase pressure and reverse flow in the leg veins, causing structural changes in the valve leaflets and vein walls. This leads to physical distortion and distention as well as transduction in endothelial cells, which promote an inflammatory and prothrombotic phenotype. Patients with a history of idiopathic deep venous thromboses or pulmonary embolus, especially at a young age, frequently have an underlying genetic thrombophilia. These inherited defects are best remembered by the mnemonic *STALL Coagulation* and include protein S deficiency, prothrombin mutation, antithrombin III deficiency, lupus anticoagulant antibodies, factor V Leiden mutation, and protein C deficiency, in addition to hyperhomocysteinemia. The mainstay of treatment for venous ulcers is compression therapy, which counters the impact of reflux, reduces blood vessel diameter and pressure, and decreases the release of inflammatory cytokines and leakage of fluid causing edema. Venous leg ulcers are addressed in greater detail in a separate chapter entitled, "Venous Ulcers."

Diabetic foot ulcers (DFU) (Figure 49-1) are another major type of chronic wound that results from complex disease-associated neuropathic and vascular changes. Diabetics have a 15% to 25% lifetime risk of developing a foot ulcer.⁶ DFUs have a high recurrence rate, frequently lead to amputation, and are associated with a high mortality.



FIGURE 49-1 Diabetic foot ulcer



FIGURE 49-2 Pressure ulcer

Many overlapping factors can lead to a DFU. Metabolic abnormalities from diabetes cause neuropathic and vascular changes. Peripheral sensory neuropathy results in loss of protective sensation that increases the risk of acute trauma or repetitive injury to an existing ulceration. Motor neuropathy affects the muscles required for normal foot movement, altering the distribution of forces during walking and causing reactive thickening of skin (callus) at sites of abnormal load. Ischemic tissue necrosis beneath the callus leads to breakdown of skin and subcutaneous tissue, resulting in a neuropathic ulcer with a punched-out appearance.⁷ The Charcot neuropathic foot of diabetes is characterized by joint deformities that also predisposes the patient to secondary ulceration. Diabetes causes ischemia from microvascular and macrovascular disease with reduced distribution of blood to skin surfaces in need of healing. Bacterial infection is an important sequela of DFU, and in turn can cause substantial deterioration of the wound and complications such as osteomyelitis that may require amputation. Management of the DFU includes wearing off-loading shoes to redistribute the weight off the ulcer site and protective footwear to prevent repeated trauma, control of infection, and revascularization procedures as indicated.

Pressure ulcers (Figure 49-2) occur most often in patients who are immobile, paralyzed, elderly, or malnourished. Pressure ulcers are caused by prolonged pressure, friction, or shear of the skin surface leading to impaired blood supply and tissue malnutrition. Tissue compression exceeding the capillary filling pressure of 32 mm Hg that lasts longer than 2 hours can cause local ischemia and necrosis.⁸ Skin overlying bony prominences including the sacrum, malleoli, or hips is particularly vulnerable. The recurrence rates of pressure ulcers may be as high as 90%. Frequent repositioning and off-loading with special beds and cushions are the cornerstone for prevention and treatment of pressure ulcers.

The most widely accepted classification system for pressure ulcers is described by the National Pressure Ulcer Advisory Panel. This four-stage classification is designed only to describe the depth of a visible ulcer at the time of examination. Stage I represents intact skin with signs of impending ulceration: blanching and/or nonblanching erythema, warmth, and induration. It is especially important to recognize and effectively treat Stage I ulcers because they can resolve, with proper care, in 5-10 days. Stage II ulcers present as a shallow ulcer (including epidermis and most often dermis) with pigmentation changes. They are usually reversible if treated appropriately. A Stage III ulcer represents the typical pressure ulcer that appears as a necrotic, foul-smelling crater. It has full-thickness skin loss with extension through subcutaneous tissue, but not underlying fascia. Stage IV ulcers represent full-thickness skin and subcutaneous tissue loss, with ulcer penetration into the deep fascia, resulting in involvement of muscle, bone, tendon, or joint capsule.

The Braden Scale is a scoring system used to predict the risk of developing a pressure sore. It is divided into six risk categories: sensory perception, moisture, activity, mobility, nutrition, and friction and shear. The best possible interpretation is a score of 23, and the worst is a six. The Braden Scale has been correlated with levels of risk based on the percentage of patients expected to develop ulcers: 15 to 18, at risk; 13 to 14, moderate risk 10 to 12, high risk; and 9 or below, very high risk.⁹ Medicare reimbursement policies have substantially changed in the last few years, and hospitals are no longer being reimbursed for treating preventable pressure ulcers. The new policy will give hospitals a strong incentive to screen patients who might be at risk and to document if the ulcer was present at the time of admission. The National Pressure Ulcer Advisory Panel (NPUAP), a nonprofit organization whose mission is to serve as the authoritative voice for improved patient outcomes in pressure ulcer prevention and treatment through public policy,

education and research, recently convened a consensus conference held at Johns Hopkins Medical Center in Baltimore, Maryland to discuss the definition of “unavoidable” pressure ulcers. The NPUAP panelists, comprised of twenty-four multidisciplinary experts, agreed that the current definition of “unavoidable” pressure ulcers developed by the Federal Government for long-term care settings captured the spirit of pressure avoidability but could not be used in all settings. Thus a revised definition was developed:

Unavoidable means that the individual developed a pressure ulcer even though the provider had evaluated the individual’s clinical condition and pressure ulcer risk factors; defined and implemented interventions that are consistent with individual needs, goals, and recognized standards of practice; monitored and evaluated the impact of the interventions; and revised the approaches as appropriate.

Furthermore, the panel agreed there are patient situations that create unavoidable pressure ulcers. For example, critical care patients with hemodynamic instability may be medically intolerant of turning or repositioning and thus develop unavoidable pressure ulcers. In addition, patients who choose not to participate in their own pressure ulcer prevention may develop “unavoidable” pressure ulcers.

Arterial ulcers (Figure 49-3) result from inadequate blood supply to the skin. Arterial insufficiency can be caused by atherosclerotic or thromboembolic disease that causes skin infarction and ulcer formation. The risk for lower extremity arterial ulcers is increased in smokers, diabetics, elderly patients, and individuals with evidence of arterial disease at other sites.⁴ Signs and symptoms include cool extremities, skin pallor, weak pulses, claudication, and rest pain. Arterial ulcers typically have a punched-out appearance and often occur distally over bony prominences. Assessment with ankle-brachial index and Doppler ultrasound for distal pulses can confirm a compromised blood supply to the limb. Treatment is aimed to promote arterial supply to the affected area.



FIGURE 49-3 Arterial ulcer

Dermatologic conditions may also result in chronic ulcers. Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that causes recurrent painful inflammatory ulcers. It is frequently associated with underlying systemic diseases, such as inflammatory bowel disease, rheumatoid arthritis, dysproteinemia, hidradenitis suppurativa, or malignancy. Pyoderma gangrenosum characteristically begins as a tender pustule that breaks down and forms an ulcer. The ulcer has a sharply circumscribed, irregular, and undermined border often with a characteristic boggy, purple appearance. Pyoderma gangrenosum ulcers occur most commonly on the lower extremities. Patients with PG demonstrate pathergy, where slight trauma to the skin can initiate a new ulcer.¹⁰ The pathogenesis is poorly understood and diagnosis is generally made on clinical grounds. Treatment of the systemic condition often leads to improvement of the skin.

Vasculitis is another dermatologic condition that causes skin ulcerations. Necrotizing inflammation of blood vessels leads to cutaneous manifestations, beginning with palpable purpura and eventually progressing to skin ulceration. Lesions are frequently painful. Vasculitides encompass a heterogeneous group and may be associated with various etiologies including autoimmune, infectious, medication-related, dysproteinemia, malignancy-related, and idiopathic. The pathogenetic mechanism involves small, medium, or large vessels and may be caused by immune complex deposition. Cutaneous polyarteritis nodosa is a vasculitis that causes a chronic relapsing course of painful nodules and ulcers.¹⁰ These ulcers are accompanied by livedo reticularis and usually occur on the bilateral lower extremities. Management involves the selection of appropriate systemic anti-inflammatories, anticoagulants, and immunosuppressants.

PRINCIPLES OF WOUND HEALING

Normal wound healing is a highly dynamic process and involves complex interactions of resident and infiltrating cells, growth factors and cytokines. The immediate goal of repair is to achieve tissue integrity and homeostasis.¹¹ To achieve this goal, an orderly, highly efficient healing process occurs in three overlapping phases: *inflammatory*, *proliferative*, and *remodeling*. The process usually takes 3 to 14 days to complete. Following hemostasis, which is achieved by platelet aggregation, the initial repair phase begins with an inflammatory response. Leukocytes infiltrate into the wound site and remove foreign material, bacteria and damaged tissue by phagocytosis. These cells, including neutrophils and macrophages, also release essential growth factors and cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor beta (TGF- β).¹² Once the wound bed is cleaned, the proliferative phase begins. Granulation tissue consisting of endothelial cells, macrophages and fibroblasts begins to form. Fibroblasts produce a collagen matrix; new blood

vessels invade the granulation tissue; and epidermal cells migrate across the wound surface to close the breach. In the final phase of remodeling, the new collagen matrix becomes cross-linked and reorganized to affect connective tissue compaction and wound contraction. Wounds gain about 20% of their final strength during these first 3 weeks of collagen deposition and, by the processes of remodeling and contraction, continue to strengthen over the following months.¹³

Nonhealing wounds often suffer from inadequate circulation, poor nutrition, compromised immune status, and lack of protection from mechanical trauma.⁴ The presence of chronic inflammation will also cause healing to stall. Clinical signs and symptoms of chronic inflammation include edema, erythema, warmth, tenderness, induration, and dyspigmentation of the affected skin. The inflammatory state features the release of proteolytic enzymes such as collagenases and elastases that destroy important healing factors like PDGF and TGF- β and degrade the connective tissue matrix.¹² The presence of chronic inflammation may lead to edema and scarring and predispose tissues over the course of years to cancer development. Compression therapy acts to decrease edema and inflammation, in order to provide a suitable environment for wound repair to take place.

Chronic wounds contain persistent microbial populations, which may function as benign colonizers or pathogenic impediments to wound healing. Bacterial populations in wounds are usually polymicrobial and include both aerobic and anaerobic organisms such as *Staphylococcus*, *Pseudomonas*, *Streptococcus*, *Escherichia*, and *Bacteroides*. When growth and death of microbes are kept in balance by host defenses, a wound is considered to be colonized. Wounds become clinically infected when host defenses are overwhelmed. These wounds often demonstrate increased erythema, edema, warmth, pain, drainage and malodor. Systemic signs, such as fever, chills, and leukocytosis suggest that the infection has progressed to cellulitis, or even bacteremia or septicemia.

Whenever possible, clinically infected wounds should be cultured and microorganism susceptibilities determined before systemic antimicrobial agents are prescribed. There are usually two available methods to collect samples for culture in the clinical setting. The first is a swab of the wound slough for qualitative culture. These results are reported as none, few, moderate, and heavy. The second is a curette sample of wound tissue for quantitative culture. The latter results are reported as the number of colony forming units (CFU) per gram of tissue. A recent study has shown that qualitative culture results do not correlate with the quantitative culture results.¹⁴ Since swabs are unreliable, quantitative culture is presently the gold standard for bacterial identification and quantification in the clinical setting. Oral antibiotics are prescribed only for meaningful positive culture results (more than 100,000 CFU per gram of tissue or clinical signs of infection). The antibiotics utilized are selected

based on antibiotic sensitivities. Commonly prescribed oral antibiotics include amoxicillin for Gram-positive bacteria, trimethoprim-sulfamethoxazole for MRSA, fluoroquinones for *Pseudomonas* and metronidazole for anaerobic organisms. Anaerobic bacteria are typically difficult to culture, but exude a distinctive foul odor from the wound. As a result, oral metronidazole is frequently prescribed empirically based on clinical suspicion. *Corynebacterium* and coagulase-negative *Staphylococcus* are normal skin flora and do not need to be treated. Patients who have systemic signs of infection require hospital admission, blood cultures, and intravenous antibiotics.

Metagenomic analysis is a novel technique to study the identity and relative abundance of bacteria in chronic wounds. The 16S rRNA gene is universal for all prokaryotes including bacteria and is not found in eukaryotes such as humans. Metagenomic analysis uses high throughput sequencing of the 16S rRNA gene to identify all the bacterial genomes in a wound sample.¹⁵ Recent data using metagenomic analysis has demonstrated greater microbial diversity, in addition to the presence of previously unrecognized anaerobic bacteria. Our analysis of a series of 40 wounds identified 15 different anaerobes by pyrosequencing compared to three different anaerobes by standard quantitative culture.¹⁶

Traditionally we think of bacteria as free-living cells, such as those floating in the blood stream causing sepsis. These bacteria exist in a planktonic state. We now understand that bacteria also exist in a biofilm state in which they form sessile groups on a surface. In addition to the slough on chronic wounds, other examples of biofilms include the soft plaque found on teeth, the accretions on indwelling medical devices, and the sludge in oil pipes.¹⁷ A biofilm is a complex community of aggregated bacteria embedded in a self-secreted exopolysaccharide matrix. Biofilms develop when individual bacterial cells that are still in a planktonic state attach to a moist surface such as a wound. The cells proliferate and form microcolonies. Once the density of bacteria has reached a certain threshold or "quorum," the bacteria begin to produce quorum sensing molecules.¹⁸ These molecules enable bacteria in the developing biofilm to communicate with each other as they organize themselves and build channels to transport oxygen and nutrients throughout the biofilm. Quorum sensing molecules are involved in both intra- and interspecies signaling. The universal molecule is considered to be autoinducer-2 (AI-2), which is used by both Gram-positive and Gram-negative organisms. Quorum sensing molecules are also implicated in the regulation of virulence factors. Biofilm bacteria have a very different phenotype and exhibit different properties from the same bacteria in their planktonic form. In addition, their self-secreted exopolysaccharide matrix serves as a substantial barrier against the penetration and activity of antibiotics and immune cells and factors. As a result, biofilms confer up to 100 to 1000 times greater resistance to traditional antibiotics and are less

susceptible to host defenses. Thus, traditional antibiotics may not be effective in treating chronic wound infections.

Novel imaging techniques have also enabled us to study the structural morphology of the biofilm in chronic wounds. Epifluorescence microscopy, which uses fluorescent stains for bacteria, can produce images of bacteria in order to visualize their location within a thick biofilm. Fluorescent in-situ hybridization (FISH) uses a DNA probe that will only bind to a specific organism. As a result, specific organisms such as *Staphylococcus*, can be located in the wound. In the future, these advanced molecular and imaging techniques will enable us to better understand wound microbiology and develop targeted therapy against biofilms in order to promote healing of chronic wounds.

There is still substantial controversy regarding the role of bacteria in impeding wound healing. We believe there is often a profligate use of oral antibiotics, leading to the dangerous promotion of antibiotic resistance, as well as wasteful spending on expensive medications that are ineffective against biofilm bacteria. As a result, research into the role of bacteria in chronic wounds is of utmost importance and urgency.

In addition to antibiotics, topical cleansers, compounds, and dressings are available to decrease the bacterial burden in chronic wounds. Antiseptics are chemical agents that are broadly toxic to microbes. Commonly used topical antiseptic solutions that should not be used on chronic wounds include hydrogen peroxide and povidone-iodine, as they are toxic to human tissue and prevent re-epithelialization of the wound. Rather, patients wishing to clean their wounds at home should do so with gentle soap and water. Other antiseptic preparations may be beneficial in appropriate situations. For example, a modified Dakin's solution at a concentration of 0.025% sodium hypochlorite elicits antimicrobial effects without harming human tissue. Antiseptic dressings include Mesalt and Xeroform. Mesalt is a hypertonic sodium chloride-impregnated gauze that is highly absorbent and discourages bacterial growth as well as inhibits overexuberant granulation tissue formation. Xeroform is an antiseptic and deodorizer gauze that is impregnated with 3% bismuth tribromophenate in petrolatum. It is less adherent than plain gauze.

A recent Cochrane review described evidence in the literature to support the use of cadexomer iodine to improve healing rates.¹⁹ Cadexomer iodine is the active ingredient in Iodosorb gel and Iodoflex. The brown paste-like compound turns white corresponding with loss of bactericidal activity after extended use, indicating the need for a new application. Cadexomer, a modified starch-based polymer bead, promotes the absorption of fluid, exudates, debris, and bacteria from the wound bed while facilitating the controlled release of iodine at levels that are not toxic to human cells. Other topical antimicrobial compounds utilized in wound care include mupirocin ointment, which is particularly effective against Gram-positive organisms, including methicillin-resistant *Staphylococcus*

aureus (MRSA), metronidazole gel, cream or lotion, which provides good anaerobic coverage, and silver sulfadiazine 1% cream commonly used on burn wounds. Neomycin and bacitracin are typically avoided in chronic wound care because of their significant potential to induce contact sensitivity.

Topical dressings that contain ionic silver are believed to be effective against bacteria in wound biofilms. An in-vitro study showed that a silver-containing hydrofiber dressing was effective in killing monomicrobial biofilms composed of *Pseudomonas aeruginosa*, *Staphylococcus aureus*, or *Enterobacter cloacae*, and a mixed polymicrobial biofilm over a contact time period of 48 hours.²⁰ Silver-containing dressings currently available include the following categories: silver foams (e.g., Mepilex Ag), silver hydrogels (e.g., Silvermed), silver alginates (e.g., Tegaderm Ag), silver hydrocolloids (e.g., Duoderm Ag), silver hydrofibers (e.g., Aquacel Ag), and silver-containing collagen dressings (e.g., Prisma). The various silver-containing dressings all possess a silver reservoir, but differ in the way in which the silver ions are released. Because silver ions, not silver atoms, produce the antimicrobial effects, silver must be present in a solution in order to exert its bactericidal properties. Therefore, dry silver dressings require contact with wound moisture in order to release the active agent. Silver ions have efficacy against Gram-negative bacteria and antibiotic-resistant organisms like MRSA and vancomycin-resistant enterococci (VRE). Silver ions kill bacteria by binding to and disrupting bacterial cell walls, damaging intracellular and nuclear membranes, poisoning respiratory enzymes, and denaturing bacterial DNA and RNA. Although some species of bacteria (*Pseudomonas* in particular) have demonstrated resistance to certain silver preparations, silver has a far lower propensity to induce bacterial resistance than classic antibiotics on account of its multitargeted mechanism of action. Disadvantages of silver products include potential irritation or discoloration of the surrounding tissues (argyria).

Hydrofera Blue is a simple and safe moist foam dressing. It contains two organic pigments with broad-spectrum bacteriostatic protection. These pigments, methylene blue and gentian violet, have been used safely in medicine for over 50 years and have efficacy against a variety of microorganisms including MRSA and VRE. Hydrofera Blue is an inexpensive option compared to other topical antimicrobial wound dressings and compounds.

TREATMENT MODALITIES

Moisture and occlusion are also important principles of wound care, which have been articulated since ancient times.²¹ Nevertheless, for nearly 2000 years, therapeutic efforts focused on drying the wound site, with absorptive gauzes as the mainstay. In the 1960s, Hinman and Maibach showed in human skin wounds that occlusion compared to air exposure resulted in more rapid re-epithelialization and

wound closure.²² Occlusion keeps moisture in the wound, which prevents dehydration of delicate new epithelial cells and allows their migration and survival on the wound. While moisture is essential for proper healing, excessive wetness on the wound bed can be problematic. Highly exudative wounds may cause maceration to the surrounding skin, resulting in tissue that appears soft, white, and friable. The macerated skin has a tendency to break down, which can delay wound healing or make the wound deteriorate further. Furthermore, fluid from chronic wounds contains biologic molecules that may actively interfere with the healing process by inhibiting fibroblast proliferation and destroying extracellular matrix. Occlusion works for other reasons as well: protection from external contamination, stimulation of collagen synthesis, creation of a hypoxic environment to promote angiogenesis and, for certain dressings, lowering the pH at the wound surface to create an environment inhospitable to microbial growth.²³

Wound dressings constitute the most basic wound management strategy. They are used to manipulate the local environment to optimize wound healing. An important goal is balancing the moisture content at the wound base. Thus, some dressings are used for absorbency of excess exudates, while others provide moisture for a dry wound base. Recent studies show that the use of occlusive dressings is also associated with fewer clinical infections, greater patient comfort, and reduced scarring. Other purposes of dressings include protection from external contamination and physical trauma, promotion of antimicrobial action on wound microbial flora, and pain relief. It is important to choose dressings that do not cause a contact allergy. Since wounds evolve over time, the appropriate dressing will need to be changed to suit the particular condition of the wound. The major categories of wound dressings include gauze, film, hydrogel, hydrocolloid, alginate, and foam. In conjunction, barrier creams, ointments, and other periwound protectants are frequently used because skin around a wound is vulnerable to damage from wound-associated inflammation, excess moisture, wound fluid proteases, dressing adhesives, and contact allergic reaction.

Plain dry cotton gauze has historically been one of the most popular wound dressings, yet it has several shortcomings. Dry gauze promotes dessication of the wound. Similarly, a wet-to-dry dressing, which involves using saline-moistened gauze that eventually dries over the wound, will stick to the wound base causing pain and trauma during dressing changes. Dry gauze also has a limited ability to protect against external contamination, especially when wound exudate has saturated the entire thickness of the gauze. A recent prospective multicentered study of 767 wounds treated using standardized dressing protocols revealed that gauze dressings compared to moisture-retentive dressings (e.g., hydrocolloids, alginates, foams) are associated with slower healing times.²⁴ Furthermore, gauze dressings are less cost effective over time even though they may be more affordable per individual dressing.

Films are transparent, adhesive, thin and semiocclusive, permitting exchange of oxygen and water vapor, but not of liquid and bacterial contaminants. Thus, films should be reserved for wounds with minimal exudate. When used as a primary dressing, transparent films allow visualization of the wound so dressing changes may occur less frequently and only as needed. When used as secondary dressings, films help secure nonadhesive dressings in place. Caution is needed when removing films because the adhesive may strip delicate new epidermis from the wound. A recent prospective open controlled study showed that film dressing is more effective than conventional treatment with ointments and gauze in the management of severe pressure ulcers.²⁵

Hydrogels are best suited for dry wounds or those with limited exudate. They are ideal for patients with painful wounds, since they can be applied and removed with minimal trauma to the wound. Patients often experience pain relief with hydrogels, likely because of their cooling effect. Hydrogels promote autolytic debridement of slough and necrotic tissue and are suitable when sharp debridement is contraindicated because of pain. Hydrogels are water-based products available in amorphous gel and sheet forms. Two sheet hydrogels frequently used in our clinic are the *Curagel* and *Xcell* brands. Recent prospective studies of hydrogel dressings have suggested their effectiveness in chronic wounds.²⁶⁻²⁷

In contrast to the fluid-donating hydrogels, hydrocolloids maintain a moist healing environment by absorption of excess exudate forming a hydrophilic gel covering. Hydrocolloids are ideal for low to moderate exudative wounds. They have a relatively long wear time and protect against shear force. A meta-analysis of 12 randomized-controlled trials comparing hydrocolloid dressings to conventional gauze dressings found that hydrocolloids improved the rate of healing in 72% of the wounds, particularly in pressure ulcers.²⁸ The most frequently used hydrocolloid in our clinic is *DuoDERM CGF*, which has a foam backing. Hydrocolloids should not be used for wounds with too much exudate because the large amount of moisture will cause the dressing to separate or cause periwound maceration. In addition, hydrocolloids have a tendency to produce a brown, malodorous drainage, which can be mistaken for infection and be troubling for the patient.

Fibrous dressings, including alginates and hydrofibers, have very high absorbency and are used for wounds with heavy exudates. Alginates are derived from brown seaweed and can hold up to 20 times their weight. Alginates require moisture to function, thus they should not be used over dry wounds. They contain calcium and sodium salts of alginic acid, a polymer of mannuronic and glucuronic acids. When placed over a moist wound, an ion exchange reaction occurs between calcium in the alginate and sodium in the wound fluid, producing soluble calcium-sodium alginate and forming a gelatinous mass. The resultant gel helps to maintain a moist healing environment. Because of

a tendency to absorb fluid across the entire surface of the dressing (lateral wicking), some alginates may cause peri-wound maceration if they overlap with normal skin. Thus, alginates should be cut to the shape of the wound bed. Several prospective, randomized-controlled studies have demonstrated that alginate dressings accelerate wound healing as compared to control dressings (e.g., gauze, dextranomer paste).²⁹⁻³⁰ A commonly used alginate in our clinic is *Silverlon*, which can be cut into strips and used to pack the tunnel in deep wounds, thus wicking the drainage out of wounds. A unique advantage of some fibrous dressings such as *Aquacel Ag* is that they are inherently hemostatic and can be used to control minor bleeding.

Foam dressings protect against shear force, provide thermal insulation, and offer different levels of absorption depending on their thickness. Some foam dressings are nonadherent, thus avoid traumatic dressing changes. Some have a film backing to prevent exudate leakage and provide an additional barrier against bacterial contamination. In studies, foam dressings are comparable to hydrocolloids in terms of ulcer healing.³¹ Like hydrocolloids, foams may promote development of excessive malodorous drainage necessitating frequent dressing changes.

Compression therapy is considered the first-line treatment for venous leg ulcers, and is also used for other wounds associated with the presence of edema and inflammation. Compression reduces edema and stasis by decreasing distention in superficial veins and assisting the calf muscle pump in venous return. It also stimulates healthier granulation tissue. The use of compression is not without risk in patients with arterial disease, which may result in ischemia because of impaired blood supply. As a result, arterial insufficiency must first be ruled out by obtaining vascular studies for arterial-brachial index (ABI) or great toe pressure. A normal ABI is in the range of 0.8 to 1.2, and an acceptable great toe pressure is above 50 mm Hg. Readings outside the normal limits should be referred to the vascular surgeon for further advice. If a patient feels significant pain or discomfort while under compression, we instruct the patient to cut off the bandage at home. We often prescribe compression stockings for patients who cannot tolerate compression bandages. Uncompensated congestive heart failure is also a relative contraindication to compression therapy.

Various forms of compression exist, ranging from multilayered bandages to stockings. The optimal pressure to overcome venous hypertension and prevent capillary exudation is generally thought to be an external pressure of 35 to 40 mm Hg at the ankle. Compression bandages can be applied up to 60 mm Hg of pressure depending on the style of the application.³² Used for both prevention of recurrent ulcers and treatment of acute ones, compression stockings can provide up to 35 mm Hg of pressure. A Cochrane systematic review of 39 randomized-controlled trials found that compression therapy was more effective than noncompression therapy for the treatment of venous

leg ulcers. Furthermore, multicomponent bandages worked better than single-component bandages. Multicomponent systems appeared to perform better when one part was an elastic bandage.³²

The Unna boot is a commonly used compression bandage, consisting of a zinc oxide-impregnated gauze wrap applied over the skin from the base of the toes to the popliteal flexure, covered with a layer of soft cotton, and wrapped with an elastic bandage that supplies compression. The zinc oxide protects the periwound skin and is thought to also enhance wound re-epithelialization and decrease inflammation. Compression boots are typically left in place for a week, although they may need to be changed more frequently if the wound is especially exudative. Proper application of an Unna boot to supply the appropriate degree of pressure requires training and experience. The tensile strength of a newly healed wound is low. As a result, it is important to continue compression, frequently at a lower pressure with stockings, for an additional 6 weeks. In addition, long-term use of compression stockings will help to prevent recurrence or new ulcers from forming.

Debridement is the medical removal of bacterial biofilm, exudate, and nonviable, unhealthy tissue, which may appear as slough or eschar, from the wound bed. There is no question that adequate debridement is necessary to improve healing because it enables normal, well-vascularized tissue to proliferate within the wound while reducing the bacterial burden and risk of wound infection. Callus, or hyperkeratosis at the rim of the wound, frequently seen in neuropathic ulcers such as DFUs also require debridement. Debridement converts chronic wounds into acute wounds, which improves ulcer bed perfusion and activates the acute wound healing response. Neutrophils and macrophages recruited to the area can then secrete growth factors and phagocytize bacteria and nonviable tissue. There are a wide range of removal techniques, which include surgical, conservative sharp, wet-to-dry, autolytic, enzymatic, maggot, high-pressure fluid irrigation, and ultrasound mist therapy. Debridement may be painful for a patient even with local anesthesia.

Conservative sharp debridement is the most rapid and precise method and is performed using a curette, scalpel, forceps, or scissors. A prospective controlled study demonstrated that chronic venous leg ulcers undergoing sharp debridement had faster healing rates and greater chance of closure compared to ulcers without intervention.³³ Sharp debridement can be used in venous, diabetic, and pressure ulcers, but caution should be exercised with arterial ulcers because ischemic tissue tends to desiccate after debridement, potentially causing ulcer enlargement.

While sharp debridement is the preferred method in our clinic, alternative techniques are also available. Autolytic debridement is a gentle process that involves rehydrating the slough and necrotic tissue in a wound to aid separation from healthy tissue. Moisture-donating dressings or the application of ointments or creams under occlusion

provide a moist environment for autolytic debridement to occur. This process may take several weeks but can be useful when sharp debridement is contraindicated, such as in patients with bleeding diatheses. A newer technique is enzymatic debridement, which uses ointments containing enzymes that break down the collagen and fibrin in wound exudates and necrotic tissue. Enzymatic debridement may also take several weeks, and examples include papain, urea, and collagenase. Current evidence suggests that *Accuzyme*, a papain-urea preparation, and *Santyl*, a collagenase, have similar efficacy.³⁴ Care should be taken to avoid application on the normal skin surrounding a wound.

Offloading, or pressure dispersion, works by spreading the pressure forces over a wide area in order to reduce pressure over the at-risk or previously ulcerated area. Offloading devices are important in the prevention and treatment of diabetic foot ulcers. The threshold for offloading (expressed as a peak pressure level or pressure-time integral), which is required to adequately heal neuropathic foot ulcers in diabetic patients is currently unknown.³⁵ Common methods to offload the foot include the following: bed rest, wheelchair, crutch-assisted gait, total contact casts, removable cast walkers, half-shoes, therapeutic shoes, custom splints, felted foam or heel lift devices, wheelchair cushions, and specialty beds including air loss beds and alternating pressure beds. Given the vast array of offloading methods, patients will need assistance from experienced practitioners to select an appropriate, cost-effective pressure redistribution device.

Although theoretically effective and frequently prescribed, crutches, wheelchair and bed rest rarely work in practice for DFU patients. Crutches often cause additional pressure to be applied to the contralateral limb, thus putting it at risk for ulceration. Wheelchairs are effective pressure reduction devices, but for many DFU patients, their homes are not designed to accommodate the bulkiness of wheelchairs. Compliance with bed rest is often difficult, especially when DFU patients do not feel discomfort or pain in their insensate foot and thus resume normal daily activities.

The gold standard for achieving pressure redistribution for DFUs is by total contact casting. The total contact cast (TCC) employs a well-molded, minimally padded cast that maintains contact with the entire plantar aspect of the foot and lower leg. The intimate fit of the cast material to the plantar surface of the foot increases the plantar weight bearing surface area to help distribute the plantar pressure from one or two distinct areas to the plantar foot as a whole. Total contact cast is quite effective in treating the majority of noninfected, nonischemic plantar DFUs, with healing rates ranging from 72% to 100% over the course of 5 to 7 weeks.³⁶ A recent randomized, controlled study compared TCC with a removable cast walker (RCW) and a half shoe. Removable cast walkers are cast-like devices that can be removed frequently to allow for self-inspection of the wound, application of topical therapies, or to bathe and

sleep more comfortably. Half shoes consist of a wedge sole that ends just proximal to the metatarsal heads to eliminate propulsive gait and dissipate ground reactive forces of the forefoot. They are commonly used because they are inexpensive and easy to apply, but are not as effective as TCCs and RCWs. This study demonstrated that patients using a TCC had far greater healing rates compared to patients using a RCW or half shoe.³⁷ Armstrong and his colleagues also observed in this study that patients treated with TCCs were significantly less active, with 600 daily steps compared to >1400 daily steps taken by those in the two other treatment groups. Furthermore, 85% of patients in the RCW and half shoe treatment groups wore the footwear most of the time while outside the home, but only 15% of them wore them at home. Thus, patient compliance and activity level appear to be important factors related to the success of offloading devices.

An innovative approach to offloading combines the clinical efficacy of TCC with the relative ease of application of the RCW. The instant total contact cast (iTCC) involves wrapping an RCW with a single layer of cohesive bandage, Elastoplast, or casting tape. The iTCC addresses the limitations of both the TCC and RCW, in that it enforces compliance and pressure redistribution while allowing for ease of application and examination of the ulcer when needed. A randomized trial comparing the standard TCC and the instant TCC found no differences in healing rates and the mean healing time between both groups.³⁸ Thus, iTCCs are comparable to the gold standard.

Pressure ulcers, frequently found in patients with spinal cord injuries or those who are bedridden because of a critical illness or poor health, also require offloading techniques for prevention and treatment. As a result of immobility, patients with sacral pressure ulcers benefit from devices that redistribute pressure while sitting or lying down for extended periods of time, such as wheelchair cushions and beds. A study comparing three commonly prescribed wheelchair cushions for pressure relief found that the Roho cushion was more effective than the Jay and Pindot cushions.³⁹ Each cushion represented the three major categories of cushion construction materials: air (Roho), gel (Jay), and polyurethane foam (Pindot). The alternating pressure air mattress (APAM) is used for bedridden patients and reduces the intensity and duration of pressure and shearing forces by alternating the area under pressure. They generate alternating high and low interface pressures between body and support surface by alternating the inflation and deflation of air-filled cells. The periodic pressure relief enables the restoration of blood supply to tissues. A review of 35 studies concluded that APAMs are likely to be more effective at relieving pressure and more cost-effective than standard hospital mattresses.⁴⁰ A Cochrane review of support surfaces for pressure ulcer prevention found that higher-tech mattresses including alternating pressure and constant low pressure mattresses have comparable effectiveness.⁴¹

Negative pressure wound therapy (NPWT), or vacuum-assisted closure (VAC), devices consist of a fenestrated evacuation tube embedded in a foam dressing and covered with an airtight film dressing. The tube is attached to a vacuum source. Sub-atmospheric pressure of – 125 mm Hg (with a range of – 50 to – 200 mm Hg depending on the nature of the wound) is applied in a continuous or intermittent manner.⁴² A canister is attached to the vacuum pump to collect the excess wound fluid. Negative pressure wound therapy dressings hasten wound healing by maintaining a moist environment, removing wound exudates, reducing bacterial loads, increasing local blood flow and granulation tissue formation, and applying mechanical pressure to promote wound closure. Another potential mechanism is the idea that microstrain, or cell stretching, stimulates cell division and proliferation in the presence of soluble mitogens, whereas retracted cells remain quiescent.⁴³

Negative pressure wound therapy technology has been in use since the 1940s. The United States Food and Drug Administration (FDA) most recently expanded the approved indications for NPWT devices, which now include chronic, acute, traumatic, subacute, and dehisced wounds, flaps and grafts, pressure ulcers, venous ulcers, and diabetic ulcers. Negative wound pressure wound therapy dressings are not appropriate for ischemic wounds because they may cause necrosis of the wound edges. They are also contraindicated for wounds associated with untreated osteomyelitis, fistulas to body cavities or organs, malignancy present in the wound, treatment that would place the NPWT over a wound with exposed arteries or veins. Wounds must be thoroughly débrided of all necrotic tissue before beginning therapy. The foam component of the dressing should be changed every other day. In some patients, dressing changes may be painful or cause trauma to the wound bed because of the in-growth of new granulation tissue into the foam; the use of denser sponges and more frequent sponge changes can help alleviate this problem.

For many years, the clinical evidence supporting the use of NPWT was based largely on clinician perception, case series, small cohort studies, and weakly powered randomized trials. The Cochrane Collection confirmed these conclusions in their review in 2000 and cited the need for more rigorous clinical trials to study the efficacy of NPWT devices. Since then, several large prospective, randomized, controlled studies have been conducted demonstrating that the wound healing rate and rate of granulation tissue formation are significantly greater with NPWT than with standard moist wound therapy (MWT).⁴⁴⁻⁴⁶

Despite the high cost of the device, NPWT has also been shown to be more economical than traditional wound care. A study of diabetic patients with postamputation wounds was performed comparing treatment with NPWT and MWT. The average total cost to achieve healing was \$25,954 for patients treated with NPWT compared with \$38,806 for the MWT group. The MWT group required more surgical procedures (including debridement), more

office visits, and more dressing changes. Thus, NPWT resulted in a greater proportion of patients who obtained wound closure at a lower overall cost of care compared to MWT.⁴⁷

Hyperbaric oxygen therapy (HBOT) is used as an adjunct to standard wound care. HBOT, which involves breathing 100% oxygen at supra-atmospheric pressures between 1.5 to 3 ATMs while inside of a compression chamber, is based on the rationale that tissue hypoxia contributes to the failure of many chronic wounds to heal. Hyperbaric oxygen therapy increases arterial oxygen pressure, which increases oxygen delivery to tissues as well as results in vasoconstriction and aids in the reduction of edema. Hyperoxygenated plasma enhances angiogenesis and ultimately collagen formation to aid in wound healing.⁴⁸ Hyperbaric oxygen therapy has also been found to be effective against anaerobic bacteria, which survive better in the body's deeper tissues. Increased tissue oxygenation also enhances leukocytes in their ability to fight infection. Hyperbaric oxygen treatments are administered 1 to 2 times daily and last 60 to 90 minutes.

The benefits of HBOT remain controversial. A Cochrane review found that the use of HBOT significantly reduced the risk of major amputation in patients with diabetic foot ulcers and that it might improve the possibility of wound healing at 1 year.⁴⁹ There was insufficient evidence to suggest benefits for venous, arterial, or pressure ulcers. In contrast, topical oxygen therapy, which involves inserting the wounded limb into an airtight bag and surrounding it with oxygen under slightly elevated pressure, is generally considered clinically ineffective.⁵⁰ Medicare reportedly reimburses HBOT as adjunctive therapy for diabetic wounds of the lower extremities if certain conditions are met, including a diabetic ulcer that is grade III or higher by the Wagner classification system and unresponsive to standard wound therapy for at least 30 consecutive days. Medicare will not continue to cover if there are no measurable signs of healing within any 30-day period of treatment.

Clinicians should first assess the degree of peri-wound hypoxia and the likelihood of favorable response to HBOT with transcutaneous oximetry prior to initiation of HBOT. The transcutaneous oxygen measurement at the wound edge should be less than 40 mm Hg. The patient's tissue response to 100% oxygen via mask should result in a transcutaneous oxygen level increase by at least 10 mm Hg.⁴⁸ A trial of HBOT should result in a transcutaneous oxygen measurement greater than 200 mm Hg. Hyperbaric oxygen therapy is associated with several potential adverse events. Absolute contraindications to HBOT include untreated pneumothorax, restrictive airway disease, and concomitant chemotherapy. Hyperbaric oxygen therapy is considered safe if the therapy does not exceed 2 hours and the pressure does not exceed three ATM. Myopia is a reversible adverse effect. Other adverse effects include otic, sinus, or pulmonary barotraumas, neurologic oxygen toxicity,

and claustrophobia. Air breaks, where oxygen breathing is interrupted, can decrease the risk of oxygen toxicity. Fire is always a risk with HBOT and safety checks are conducted prior to entering the chamber.

Growth factors and skin substitutes are among the most recent advances in wound care. Growth factors control many of the key cellular activities involved in the normal tissue repair process, including cell division, cell migration, angiogenesis, and synthesis of extracellular matrix components. Some have suggested that a deficiency of growth factors may exist in chronic wounds. Thus, investigators have examined the benefits of exogenous growth factor application for wound healing. Recombinant human platelet-derived growth factor isoform BB or becaplermin is the only topical growth factor approved by the FDA for the treatment of chronic wounds, indicated for use on chronic neuropathic lower extremity diabetic ulcers. The biologic activity of becaplermin is similar to that of endogenous PDGF-BB, in that it promotes the chemotactic recruitment and proliferation of cells involved in wound repair. Be caplermin has been shown to increase the number of completely healed ulcers at 20 weeks compared to placebo in four multicentered, prospective, randomized, controlled trials.⁵¹

Tissue engineered skin substitutes use living cells, such as fibroblasts and keratinocytes, in a scaffold or natural or synthetic extracellular matrices. The goals of skin substitutes include wound coverage, complete wound closure, reduced healing time, reduced pain, reduced postoperative contracture, and improved aesthetics and functional abilities. Dermal skin substitutes help prevent wound contraction and offer greater mechanical stability. Examples include bovine collagen and Dermagraft, a cryopreserved dermal substitute composed of fibroblasts that is indicated in the treatment of full thickness DFUs greater than

6 weeks duration. Combined dermal and epidermal skin substitutes include Apligraf, an allogeneic, bilayered skin substitute containing both keratinocytes and fibroblasts in a bovine collagen I matrix. Multicentered prospective, randomized clinical trials have demonstrated that Apligraf in conjunction with standard compression therapy is well tolerated and more efficacious in patients with VLUs when compared to compression therapy alone, especially in patients with full-thickness ulcers of >6 months duration. In addition, Apligraf in conjunction with standard diabetic foot care is well tolerated and superior in efficacy, when compared to diabetic foot care alone for refractory full-thickness neuropathic diabetic foot ulcers.⁵²

New biologics that are currently in the pipeline include a suspension of living, growth-arrested, allogeneic keratinocytes and fibroblasts cultured from neonatal foreskin in a fibrin gel for venous leg ulcers. Similar research involves a reconstructed skin substitute made with the patient's own cells. DERMAGEN, a sponge composed of collagen and glycosaminoglycans, reticulated by ionic bonds with chitosan before freeze-drying, is another novel dermal replacement under investigation. This substitute, cellularized by functional allogeneic fibroblasts, is being tested in patients with diabetic foot ulcers.⁵³

CONCLUSION

Wound care represents a great opportunity for dermatologists who are the "skin" doctors, especially when half the total health care budget is spent on wounds every year and most of the reimbursements are paid to other types of healthcare providers. In addition, the staggering expenditures related to chronic wounds continue to burden our health system and will only worsen as obesity and diabetes become more prevalent in the ageing population.

What We Know

- Chronic wounds cause significant morbidity and are a major healthcare burden. Almost \$25 billion per year is spent on the treatment of chronic wounds, which represents greater than 50% of all skin care expenditures in the United States.
- Chronic wounds fail to proceed through the orderly and timely process of repair. The etiologies of chronic wounds are wide ranging and include venous insufficiency, diabetes, physical immobility, arterial disease and a myriad of dermatologic conditions such as vasculitis and pyoderma gangrenosum.
- Chronic wounds contain persistent polymicrobial populations, which affect wound healing. Bacteria in chronic wounds form in a biofilm, a complex community of aggregated bacteria embedded in a self-secreted

exopolysaccharide matrix. Traditional antibiotics are inadequate therapy against biofilm in chronic wounds.

- Current treatment modalities for chronic wounds include moisture and occlusion with appropriate wound dressings, compression, debridement, offloading, negative pressure wound therapy, hyperbaric oxygen therapy, growth factors and skin substitutes. Appropriate therapeutic choice depends on many factors including the specific type of ulcer, the nature of the ulcer base, the presence of bacteria, the vascular supply, and the general health and underlying disease status of the patient.
- Wound care represents a great opportunity for dermatologists to develop more expertise in both its clinical and research frontiers.

The wide variety of etiologies and available treatment modalities make ulcers a complicated diagnostic, therapeutic, and investigative endeavor. Research is still ongoing for evidence-based practices and much work remains in developing suitable protocols to diagnose and treat chronic wounds. Dermatologists are the skin biologists yet much of the wound research conducted is by researchers with limited experience in skin disease. More education is needed to remedy the dearth of wound care expertise among dermatologists in the United States. Medical dermatology has a major responsibility to shape the future of care for skin ulcers.

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Treatment of Venous Leg Ulcers

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INTRODUCTION

Venous leg ulcers are commonly encountered in the medical practice, and treated by a diversity of healthcare professionals and physicians of various medical specialties, including dermatologists. While a wide variety of devices, dressings, and other products have been used to treat venous leg ulcers, many of these treatments lack a high level of evidence to support their use. The objective of this chapter is to present the evidence for the commonly used treatments for venous leg ulcers.

EPIDEMIOLOGY

Venous leg ulcers are both prevalent and costly. Venous ulcers represent up to 80% of lower leg ulcers in the United States and a single venous ulcer costs approximately \$27,493 for people treated with standard care.^{1,2} Overall, care for a venous ulcer represents 1% of the U.S. healthcare budget. The prevalence of venous ulcers increases with age and is higher among women.³ The estimated lifetime prevalence for leg ulceration in developed countries is 1%.⁴ The UK Healthcare Commission has estimated that currently leg ulcer care costs the NHS £300-600 (€330-661, \$447-895) a year.⁵ However, even in those successfully treated, venous insufficiency is a life-long disease and recurrence is common. Recurrence is reported to be high; up to 37% - 48% at 3 and 5 years, respectively.^{6,7}

PATHOPHYSIOLOGY

The venous system in the legs is comprised by the deep venous system that is supported by the calf muscles, the superficial system that lacks external support, and the communicating veins that connect both systems. Leg veins have one-way valves that normally cause the blood to flow from the extremities to the heart. Failure of the calf muscle pump, by either venous disease (valve dysfunction) or failure of other components of the muscle pump can lead to sustained ambulatory venous pressure (venous hypertension). Venous hypertension leads to dilation and elongation of the veins and venules, disruption of microcirculation

with increasing permeability and leaking of plasma and red blood cells into the tissue.⁸⁻¹¹

Sustained pressure in the venous system leads to venous pooling, tortuosity, and increased hydrostatic pressure in capillaries.

Clinically patients present with edema and an aching pain in the affected limb, worse at the end of the day and with dependency, and improved with leg elevation.¹² This is the typical presentation of Chronic Venous Disease and one important consequence of this process is the formation of a venous leg ulcer.¹³

Increased ambulatory venous pressure causes leukocyte trapping in the postcapillary circulation, resulting in leukocyte margination and activation releasing proteolytic enzymes, free radicals, cytokines such as TNF α , interleukin 1, and leukotrienes. It all results in inflammation and tissue hypoxia. Damage to vessels leads to increased endothelial spaces, extravasation of matrix proteins, such as fibrinogen, which leads to a pericapillary fibrin cuff, and trapping of growth factors within the cuff.¹⁴⁻¹⁹

This cascade of events is thought to set the environment for skin changes and eventually ulceration. Getting to know the pathology of venous ulceration, several treatment alternatives have emerged some of them still under research and some of them already proven effective.

DIAGNOSIS

The diagnosis of a venous leg ulcer can often be made by the clinical appearance of the leg and associated wound. The classic presentation of a venous leg ulcer is an irregularly shaped wound with well-defined borders, surrounded by erythematous or hyperpigmented indurated skin. Venous ulcers are not deep and the presence of exposed tendon or bone suggests alternative diagnoses. The indurated fibrotic surrounding tissue is termed chronic lipodermatosclerosis. Within the ulcer bed, a yellow-white exudate is commonly observed. Venous ulcers vary in size and location, but are usually found on the distal medial aspect of the lower leg ("gaiter" area). A lateral venous ulcer may be associated with short saphenous insufficiency. Varicose veins are often present in the venous ulcer patient. Typically, there are telangiectatic veins of the medial ankle, so-called corona

phlebectatica, and indicative of chronic venous insufficiency. Edema of the ankle area is common, although as mentioned above in some patients, the skin is fibrotic and as a result the ankle circumference is actually narrowed.²⁰ Confirmation of the venous disease is desirable and color duplex ultrasound scanning is useful in providing anatomic and physiologic data, helping to confirm venous disease and possibly a venous etiology for the leg ulcer.²¹ However, it must be recognized that venous disease may occur in wounds of various etiologies.

Among the common causes of lower extremity ulceration, there are neuropathic (diabetic) ulcers, arterial ulcers, pyoderma gangrenosum, neoplasia, vasculitis, sickle cell anemia ulcers, and venous leg ulcers. Each condition has its own characteristics that should be considered when making a differential diagnosis and in the overall management of the patient when more than one condition exists.

SEARCH METHODOLOGY

Pubmed and the Cochrane Database for Systematic Reviews were searched for “venous leg ulcers” and “treatment”; wound groups guidelines and relevant bibliographies were reviewed.

RESEARCH QUESTIONS AND ANSWERS

Several interventions have been used in the approach to venous leg ulcers. Figure 50-1 shows an evidence-based algorithm of treatment to this condition. In this chapter, we will describe each one of these interventions as well as other alternatives that have been used, even in the absence of evidence.

COMPRESSION

The primary cause of venous ulceration is venous hypertension. Venous hypertension is defined as the increased hydrostatic pressure in the venous circulation that is caused by a diseased venous system or failure of the calf muscle pump. While in normal persons, ambulation and resultant return of venous blood reduces pressure in the venous system, in venous hypertension, pressure of the deep system may fall either minimally or not at all during ambulation. This increased pressure may be then transmitted to the superficial system. The term sustained ambulatory venous hypertension more accurately describes the condition known as venous hypertension.¹ Venous hypertension is associated with venous ulceration. Compression is meant to reverse the effects of increased hydrostatic pressure in the leg veins. Compression works, in part, by relieving the edema caused by local hydrostatic pressure. Additionally it is thought that compression also has an effect in lymph propulsion and enhances fibrinolysis. Compression helps venous return, even in patients with incompetent valves by approximating the valve leaflets.¹ The external pressure

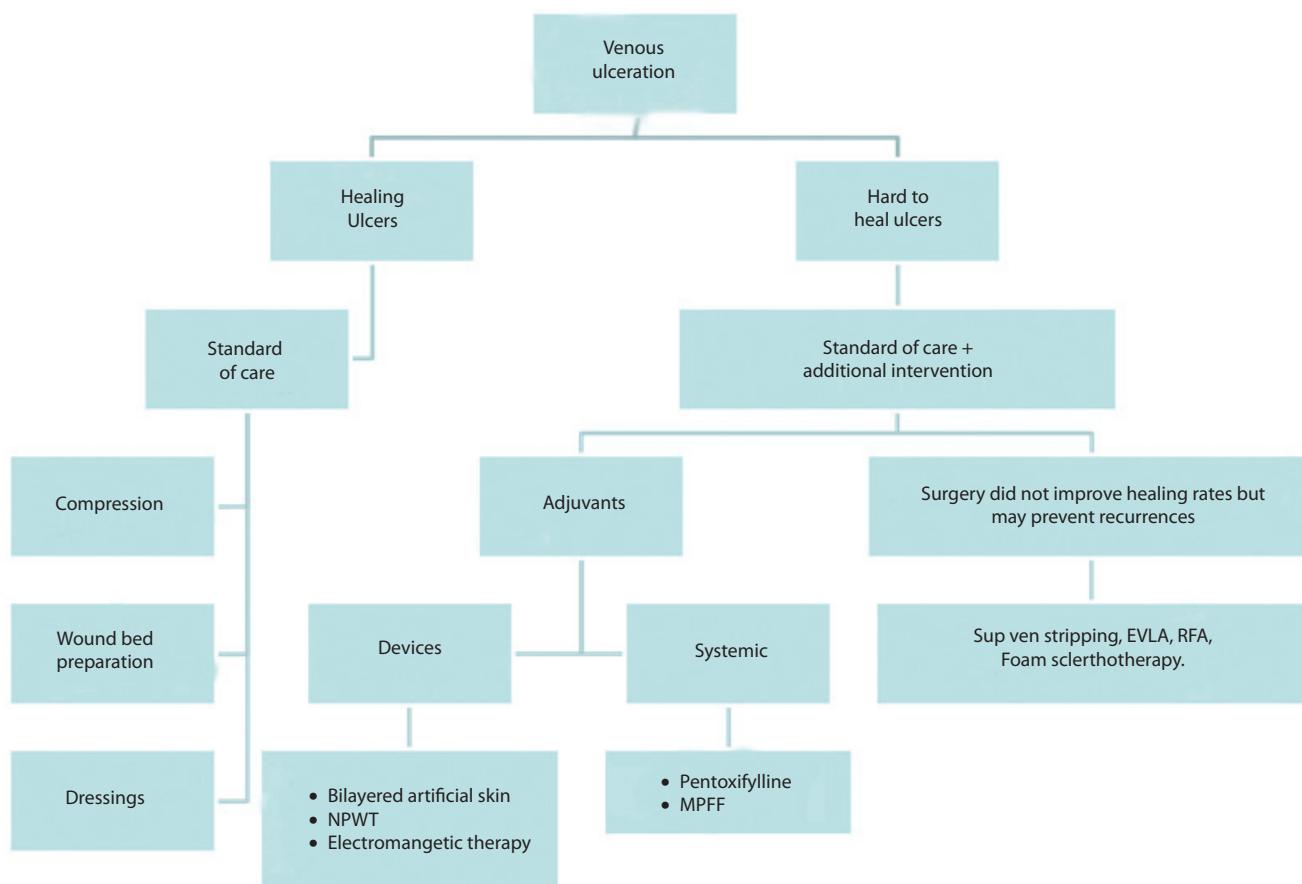
applied is not well defined but is generally agreed that 30 to 45 mm Hg at the ankle would overcome hydrostatic pressure and prevent capillary exudation.²² There are several modalities to achieve this goal, they are similar in effectiveness but can differ significantly in comfort and cost.²³ Two phases of compression exist in the treatment of venous leg ulcers, the first is edema management and the second is maintenance compression.¹

Three broad groups of compression alternatives exist: elastic compression, inelastic compression, and intermittent or pneumatic compression. Elastic compression provides working and resting pressure caused by elasticity of the stretch bandages; this kind of compression can be used in the initial and ongoing treatment of venous ulceration.^{1,22} The ankle-brachial index or ABI is the ratio of the systolic blood pressure in the ankle over that in the arm (brachial) and is used to assess peripheral arterial disease. In the supine patient, the normal value is 1 and is reduced in patients with arterial disease of the lower limb. The more severe the arterial disease is, the lower the ABI. As mentioned it is critical to adequately assess arterial flow before applying elastic compression, as excessive compression can be harmful in a poorly perfused limb. The cut-off point for application of elastic compression, used in many studies is an ABI of 0.8.²³ In some cases with minimal arterial disease, inelastic compression can be used. Prototype for inelastic compression is the Unna boot. Inelastic compression provides high working pressures but does not provide compression in a resting limb, so its effectiveness depends on the patient ambulation but it is safer because of this. This modality of compression is helpful during the edema management phase and is an alternative in patients with peripheral arterial disease. Intermittent or pneumatic compression can be used with or without compression dressings and can provide another option in patients that are not candidates for another compression modality.²³

Once the ulcer is healed, maintenance compression with stockings is necessary in the long term to prevent venous ulcer formation.²⁴ There are four classes of compression stockings based on the compression exerted at the ankle. Compression class I stockings exert an ankle pressure of 20 to 30 mm Hg and are indicated for varicose veins, mild edema, or leg fatigue. Compression class II stockings are 30 to 40 mm Hg and are indicated for moderate leg edema, severe varicosities, and moderate venous insufficiency. Compression classes III (40-50 mm Hg) and IV (≥ 60 mm Hg) are indicated for severe edema or elephantiasis and severe venous insufficiency with secondary post-thrombotic edema.¹

What is the evidence for Compression when treating and preventing venous leg ulcers?

The evidence from a systematic review by the Cochrane collaboration suggests that venous ulcers heal more rapidly with compression than without compression and that



NPWT: Negative pressure wound therapy. MPFF: Micronized purified flavonoid fraction, Sup ven stripping, Superficial venous stripping/ EVLA: Endovenous laser ablation, RFA: Radio frequency ablation.

FIGURE 50-1 Venous leg ulcers: Evidence based algorithm of treatment.

multi-component systems achieve better healing outcomes than single-component compression.²³ When competing systems comprising two components were compared, there was some evidence suggesting that those including an elastic component may be more effective. The data suggest that costs associated with compression treatment are lower than those for strategies not involving compression.²³

Recently a multicenter study in Germany compared short stretch bandages with U-stockings in 121 patients. U-stockings are a type of compression that has two overlapping stockings with graduated compression, and when applied are additive in compression applied. In this study, complete healing within 12 weeks was found in 47.5% patients using the U-stockings compared to 31.7% using short stretch compression group ($p=0.0129$).²⁵

A group called VenUS studied 387 patients using two different compression modalities for 12 months. One group received a four-layer bandage and the other group a short-stretch bandage. They found that ulcers in the short-stretch bandage group healed in a mean of 126 days and those in the four-layer bandage healed in 92 days. Additionally, a difference of 34 days in the median time to healing between

groups was observed. Wounds healed in 76.5% of patients using the short-stretch bandage compared to 80.5% using four layer bandages, but the difference was not statistically significant.^{26,27}

Recently published Guidelines state that pneumatic compression devices appear to have improved outcomes and should be considered in combination with compression in nonresponding ulcers.²¹

Evidence-based guidelines present evidence that patients with signs of increased ambulatory venous pressure and/or postphlebitic syndrome should use compression stockings regularly and forever.²⁴

WOUND BED PREPARATION

Wound bed preparation is defined as the management of the wound to accelerate endogenous healing or to facilitate the effectiveness of other therapeutic measures.²¹ The rationale for debridement is focused on removing nonviable tissue, decreasing bacterial burden, and stimulating epithelialization.²⁸ Debridement is envisioned to remove nonviable tissue (necrotic, pus, slough, callus), thereby promoting

granulation tissue formation. The result is anticipated to be an epithelializing edge and the removal of infected and possibly fibrotic tissue. Initial debridement tends to be a more extensive removal of nonviable tissue. Debridement to improve the wound bed even when the wound bed may appear clinically adequate has been suggested to control the bacterial bioburden, and stimulate healing and it has been mentioned as maintenance debridement.²⁹

Several methods of debridement exist. Autolytic debridement is achieved using occlusive or semiocclusive dressings (material and properties are selected according to a particular patient or wound characteristics). This method uses the patients own wound tissue fluid, which contains proteolytic and other enzymes for debriding the wound base. It is relatively painless and is specific for nonviable tissue.

Chemical debridement uses agents with enzymatic properties to remove necrotic tissue and the formation of healthy granulation tissue. In the United States, agents currently available include collagenase, papain, and trypsin.

Mechanical debridement includes wet-to-dry dressings, hydrotherapy, irrigation, sharp debridement, with the latter most commonly employed and thought to be most advantageous. When performing sharp debridement, certain considerations regarding anesthesia, analgesia, and bleeding should be taken in account.²⁸

What is the evidence for wound bed preparation when treating venous leg ulcers?

Limited data exists to support debridement for venous ulcers. The importance of debridement stems primarily from treatment of diabetic foot ulcer, where debridement initially was supported from secondary analysis of a randomized, double blind, placebo-controlled, multicenter trial of the safety and efficacy of topically applied Rh PDGF, in the treatment of chronic diabetic ulcers. In this analysis, it was found that centers performing the most frequent debridement had the highest wound closure rates in both the treatment group and placebo treatment groups. Similarly, the centers that performed the least frequent débridements had the lowest healing rates.²⁹

Despite limited data, expert opinion supports debridement and it has been included in various venous ulcer guidelines. These guidelines state that sharp debridement is often the most advantageous. However, the chosen method depends on the status of the wound, the capability of the health provider, the overall condition of the patient and professional licensing restrictions.²¹

DRESSINGS

Once the wound has been prepared and before the leg is compressed, it is necessary to assure a proper wound

environment for the ulcer to heal. The ideal situation would be to keep a moist wound base, rid the wound of excessive proteases, inflammatory cytokines, and harmful bacteria.

Two papers published in the 1960s provided evidence for the concept that wounds had faster re-epithelialization when exposed to a moist local environment, as opposed to being allowed to desiccate when uncovered.²² However, on the other hand, studies have showed that fluid from chronic wounds may be detrimental to cellular proliferation because of its altered levels of proinflammatory cytokines, including interleukin-1 and 6, and tumor necrosis factor alpha.³⁰

In order to keep a balanced wound environment, there are many options for wound dressings. Table 50-1 summarizes the available dressings.

What is the evidence for dressings in the treatment of venous leg ulcers?

A recent systematic review included 42 randomized-controlled studies that compared the effectiveness of hydrocolloids, foams, alginates, hydrogel dressings and a group of miscellaneous dressings. No evidence was found that any one dressing type was better than others with regard to complete healing were. The most common dressing studied was a hydrocolloid dressing. Current evidence did not find that hydrocolloids are more effective than simple low adherent dressings used beneath compression with regard to healing. Due to limited data, other comparisons were found to have insufficient evidence.³¹

A randomized, open, controlled, multicenter, multinational trial in venous leg ulcers compared cadexomer iodine paste, hydrocolloid dressing, and paraffin gauze

TABLE 50-1—Dressings for the Treatment of Venous Leg Ulcers

Moisture control	Bacteria control	Proteases control
<u>Severe exudate</u> <u>Alginates</u> <u>Foams</u>	Cadexomer iodine	Homogenous mixture of 55% bovine collagen and 45% oxidized regenerated cellulose
<u>Moderate exudate</u> <u>Collagens</u> <u>Foams</u>	Silver dressings	Sulfonated polymer dressing with the ability to bind and inactivate proteases
<u>Minimal exudate</u> Hydrocolloids Transparent films	Methylene Blue and Gentian Violet	
Poor moisturized wound Hydrogels	Polyhexamethyl biguanide and chlorhexidine gluconate	

dressing and short-stretch compression bandages throughout the study. A total of 153 patients entered the study and were treated for 12 weeks or until cessation of exudation. The study found the healing rate was significantly higher for cadexomer iodine than for paraffin gauze and that was more cost effective than hydrocolloid dressing or paraffin gauze.³²

Another open, multicenter, block-randomized and controlled study included fifteen centers in seven countries, studied performance of silver foam dressings plus compression versus foam dressings for 4 weeks (a surrogate endpoint), plus compression. This study found the silver-releasing dressing to reduce the wound area significantly faster than the traditional dressing, as well as decreasing odor, leakage, and maceration, suggesting good exudate management capabilities of the silver-releasing dressing.³³

Current recommendations conclude that when choosing the adequate dressing, the cost-effectiveness should be considered while managing the local exudate but keeping a moist environment, preventing maceration, and taking in account the particular susceptibility to contact dermatitis in venous leg ulcer patients.²¹

SURGERY

Despite compression therapy, a group of patients exists whose ulcers are refractory to treatment. To address nonhealing wounds, surgical approaches have been used to treat the ulcer and the surrounding tissue with excision and grafting, as well as techniques that address the diseased venous system.

Venous Surgery

The surgical approaches that exist for venous insufficiency have been developed depending on the anatomic location of the condition. Different surgical procedures exist for the superficial system (saphenous), perforators and deep venous system. Table 50-2 summarizes the surgical approaches used in venous insufficiency.

Radical excision and free flap

This technique consists of the radical excision of the ulcer bed, the fibrotic suprafascial tissues, and the diseased superficial and perforating veins. This is often accompanied with coverage of the large soft tissue defect with a free flap.¹

No randomized-controlled trials for these procedures exist but Kumins et al. reported their experience treating 22 patients. They performed 25 free tissue transfers (23 muscles and 2 omentum) in 22 patients. Free tissue transfer was successful in 24 (96%) of 25 flaps and the last case healed after a second flap was performed.³⁴

Kawamura et al. evaluated retrospectively eleven patients who underwent free and pedicled flap transfer

TABLE 50-2—Venous Insufficiency Surgical Approaches

Superficial System (Saphenous) Reflux Treated with Superficial Venous Surgery

1. Saphenous vein stripping
2. Endovenous laser ablation (EVLA)
3. Radiofrequency ablation (RFA)
4. Ultrasound guided Foam sclerotherapy (UGFS)
5. Transilluminated powered phlebotomy

Backflow of the Deep System to the Superficial System Treated with Perforator Surgery

1. Subfascial endoscopic perforator surgery (SEPS)
2. Linton and Cockett procedure

Deep-Vein Incompetence Treated with Valvuloplasty

1. Percutaneous vein valve bioprosthesis

for treatment of intractable venous ulcers. No ulcer recurrences were noted in the territory of the transferred flap after a mean of 11 years during follow-up. However, four patients developed new ulcers in the same leg after the flap transfer at 18, 24, 52, and 81 months, respectively. It was proposed that these patients were recurrent because of incomplete excision of surrounding lipodermatosclerotic tissue.³⁵

Skin grafting

Skin grafts have been used to treat venous ulcers. These grafts can be derived from a variety of sources including from the patient's own intact skin (autograft), from a donor-cultured cells as bioengineered skin (allograft) and also from an animal donor (xenograft). Bioengineered skin is considered a device and will be reviewed later in this chapter.

Autograft techniques can be divided into split thickness skin graft (STSG), and full-thickness grafts. STSG consist of skin with epidermis and part of the dermis.

Kirsner et al. reported an analysis of venous leg ulcers treated with meshed STSG. While the majority 'took', 52% of ulcers remained healed after 3 months, 26% were partially healed, and 22% recurred. This study concluded that meshed split-thickness skin grafting is a safe and effective therapy for recalcitrant lower extremity ulcers.³⁶

However, a recent meta-analysis investigated the effect of applying a skin graft in healing a venous ulcer when compared to standard care. It concluded that there is not enough evidence to support the use of skin grafting when treating venous leg ulcers.³⁷

What is the evidence for Surgery to treat venous leg ulcers?

Vein Surgery

The ESCHAR (Effect of Surgery and Compression on Healing and Recurrence) study was a randomized-controlled trial

of venous intervention. The results found that superficial venous surgery does not speed healing but does prevent recurrence when added to compression.³⁸ In the venous surgery group, 12% of ulcers recurred compared to 28% in the compression alone group. The intervention used was superficial venous stripping but did not include ELA, RFA, and foam sclerotherapy.³⁷ The precise role of perforating vein surgery is not well defined at present but is often used in combination with superficial venous surgery, where incompetent calf perforating veins are identified by duplex ultrasound imaging. This procedure is not suitable when the patient has severe deep venous disease with either deep reflux or obstruction.^{21,39}

Regarding surgical valve repair, a meta-analysis found that selected patients can benefit from surgical valve repair, femoral vein transposition, or venous segment transplantation, but the majority of patients with deep valve incompetence with obstruction or residual thrombus are not candidates for these procedures. This treatment achieves moderate and sustained clinical improvement but clinical data is insufficient for general recommendations.⁴⁰

Radical excision and free flap

There is no evidence that supports recommendations for this procedure. Currently there are no definite indications for this intervention and cost and morbidity are a matter of consideration.¹

Adjuvant Therapy

These are additional methods developed to help those ulcers that fail to conventional treatment.

ARTIFICIAL SKIN

One bilayered skin substitutes is FDA approved for the treatment of venous ulcers. The bilayered skin substitute is a skin construct containing an outer live allogeneic human keratinocytes, overlying a layer of live allogeneic fibroblasts placed in type 1 bovine collagen. Both cell types are harvested from neonatal foreskin.²⁸

What is the evidence of Artificial skin grafts when treating venous leg ulcers?

A Cochrane meta-analysis³⁷ found 15 trials that studied separately autografts, allografts, xenografts, bilayered artificial skin, and single layer artificial skin. Two studies that compared bilayered artificial skin versus standard of care were found. Falanga, 1998 treated 154 patients with bilayered artificial skin and 155 patients with a dressing, after 6 months 63% patients from the treatment group had healed compared to 49% of the control group. Brown-Etris, 2000 treated 17 patients with bilayered artificial skin and 19

patients with a dressing, after 6 months 71% of the patients in the treatment group had healed compared to 37% in the control group. Pooling the results of these studies, found a relative risk of healing (RR) of 1.51, suggesting the use of bilayered artificial skin helps healing in venous leg ulcers. This meta-analysis found one study that compared bilayered artificial skin with an autograft, it involved 12 ulcers and no difference was found between the groups.

There was not enough evidence from the other trials analyzed by Cochrane to determine whether other types of skin grafting increased the healing of venous ulcers. Further research is needed to assess whether other forms of skin grafts increase ulcer healing.³⁷

Cultured epithelial autografts or allografts in randomized-controlled trial have not been demonstrated to improve healing of venous ulcers.²¹

Vacuum-assisted closure (VAC) or negative pressure wound therapy (NPWT) or yopical negative pressure (TNP)

This therapy consists of an adhesive sealed dressing on the wound that is connected to a vacuum machine; it creates continuous or intermittent negative pressure about -50 mm Hg to -125 mm Hg.⁴¹ The postulated mechanisms of action are to remove excessive exudate, to enhance the capillary flow and vascular perfusion, to remove slough, to reduce the bacterial burden and to create mechanical stress that physically and biologically alter cells, to stimulate angiogenesis and tissue growth.⁴²

What is the evidence of vacuum-assisted closure when treating venous leg ulcers?

Current guidelines point that experience in venous ulcer regarding NPWT is limited but it may be useful prior to a skin graft or flap for granulation tissue development, or postoperatively by preventing shearing and removing exudates.^{21,41}

ELECTROMAGNETIC THERAPY

Electromagnetic therapy applies pulsed short wave electrical current to the wounded tissue using different voltages. It is hypothesized that electrical stimulation influences the migratory, proliferative and synthetic functions of fibroblasts, and also results in increased expression of growth factors. A moist wound environment is essential to maintain the flow of an endogenous or applied current.⁴³

What is the evidence of electromagnetic therapy when treating venous leg ulcers?

A recent Cochrane meta-analysis reviewed three studies on this topic. Ieran in 1990 treated 22 patients with

electromagnetic therapy and 22 with sham therapy. Follow-up was lost in three and four patients of each group respectively. After 90 days, a 67% healing rate in the treatment group and 32% healing in the control group was found. These results may be biased because the ulcer size in the control group was larger than the treatment group. Kenkre 1996 treated 10 patients with electromagnetic therapy and nine with sham therapy, after 50 days 20% of ulcers healed in the treatment group and 22% of ulcers healed in the control group. Stiller in 1992 compared electromagnetic therapy with topical therapy and found at eight weeks that 47% of ulcers in the treatment group reduced its size and 49% of ulcers in the control group increased its size. These studies were underpowered and methodologically weak, their results were not pooled because of differences in each other's design. Electromagnetic therapy requires further evaluation in larger, well-designed studies. Future trials will require a well-designed protocol to achieve reliable results.⁴³

Current guidelines state that electromagnetic therapy may be useful in reducing the size of venous leg ulcers. Data regarding whether the electrical stimulus should be high voltage, low voltage, or pulsed and whether AC or DC current is superior is not available.²¹

LASER THERAPY

For wound healing, gas lasers such as Helium Neon (HeNe) and Gallium Arsenide (GaAs) are used for biostimulation. The proposed mechanism of action is increased protein synthesis and the proliferation of cells such as fibroblasts and macrophages associated with wound healing.⁴⁴

What is the evidence of laser therapy when treating venous leg ulcers?

A meta-analysis included four studies and did not demonstrate a statistically significant improvement in venous leg ulcer healing with the use of low-level laser therapy. The only suggestion of therapeutic benefit is shown in one small RCT where a combination of laser and infrared light, led to an improvement in the healing rates of venous ulcers.⁴⁴

ULTRASOUND THERAPY

This therapy delivers ultrasonic energy to the wound bed, producing a thermal effect that has been hypothesized as capable of increasing blood flow, and might produce in the physical attributes of collagen-rich structures; a vibration effect may also lead to alteration of cellular or tissue structures.⁴⁵ However, the most important effects of ultrasound treatment is cavitation, which is the occurrence of oscillating "bubbles" which lead to alteration or disruption of cell membranes and other, noncellular structures and has a debriding effect.⁴⁶

What is the evidence of ultrasound therapy when treating venous leg ulcers?

There is insufficient evidence in this review to support the routine use of therapeutic ultrasound in practice. The available evidence suggests that there may be a benefit from ultrasound therapy in healing venous leg ulcers, however because of quality issues of the studies included results should be interpreted with caution.⁴⁵

HYPERBARIC OXYGEN THERAPY (HBOT)

The rationale for hyperbaric oxygen therapy is that, despite the wide range of causative pathologies, the common denominator in many wounds is tissue hypoxia. Some elements of tissue repair are extremely oxygen dependent, for example collagen elaboration and deposition by fibroblasts and bacterial killing by macrophages. Certainly, wounds that lie in hypoxic tissue beds are those that most often display poor or absent healing.⁴⁷

What is the evidence of hyperbaric oxygen therapy when treating venous leg ulcers?

Hyperbaric oxygen therapy is currently used as an adjuvant therapy in many types of chronic wounds, a meta-analysis found one trial made in venous ulcers finding wound size reduction and healing rate improvement in the treated group and suggesting a benefit of HBOT, however, no conclusive data is available yet to recommend this approach when treating venous leg ulcers.⁴⁷

SYSTEMIC AND TOPICAL ADJUVANTS

Pentoxifylline

Pentoxifylline, a xanthine derivative, improves blood flow properties by decreasing blood viscosity, has hemorheologic properties, increases red blood cell membrane flexibility, increases leukocyte deformability and inhibits neutrophil adhesion and activation. It also inhibits tumor necrosis factor-alpha synthesis and improves tissue oxygenation. Relatively safe and well tolerated, its adverse effects are mainly gastrointestinal disturbances.⁴⁸

It is approved for intermittent claudication and several studies support its use in other areas including venous leg ulcer management.

What is the evidence for the use of pentoxifylline in venous leg ulcer treatment?

In a recent meta-analysis of twelve trials involving 864 participants with venous leg ulcers, it was found that pentoxifylline is effective in promoting leg ulcer healing

when used in combination with compression treatment. It was also found in a subgroup of hard to heal ulcers, that pentoxifylline may be effective in VLU healing without compression, which may result in an alternative tool in patients that are unable to use compression. The data also suggests a cost savings.⁴⁹

The optimal dose of pentoxifylline may be higher than used for claudication. A prospective, randomized, double-blind, multicenter, placebo-controlled study randomized 131 patients all with compression therapy to pentoxifylline 400 mg, pentoxifylline 800 mg, or placebo tablets three times a day. The median time to healing was faster with pentoxifylline in a dose-dependent fashion. Venous ulcer healing was found to be 100 days for placebo, 83 days for pentoxifylline 400 mg TID, and 71 days for pentoxifylline 800 mg TID, suggesting not only that pentoxifylline accelerates healing of leg ulcers but also that a higher dose is more effective than lower dose.⁵⁰

MICRONIZED PURIFIED FLAVONOID FRACTION

Micronized purified flavonoid fraction (MPFF) is an orally delivered compound, consisting of 90% diosmin and 10% flavonoids (hesperidin). MPFF has an effect on venous, lymphatic, and capillary circulation. MPFF decreases the interaction between leucocytes and endothelial cells by inhibiting expression of endothelial intercellular adhesion molecule 1 (ICAM-1), and vascular cell adhesion molecule (VCAM), as well as the surface expression of some leucocyte adhesion molecules, MPFF presumably acts through an anti-inflammatory mechanism. There are few known side-effects, and interactions with other drugs have not been reported, it is currently indicated for venous and hemorrhoidal disease.^{51,52}

What is the evidence for MPFF in the treatment of venous leg ulcers?

Data from small studies support MPFF use in VLU treatment. A meta-analysis was published that studied the use of micronized purified flavonoid fraction (MPFF) combined with compression treatment.⁵¹ The mean healing time was 16 weeks in patients treated with MPFF plus compression compared to 21 weeks in patients with compression alone. Combined data showed an average duration of the ulcer was 13.5 years and the average size was 10.4cm.^{2,51} In the absence of studies that compare MPFF effect in smaller and shorter duration ulcers, it is thought that MPFF be considered an adjuvant in long-standing and larger ulcers.

ASPIRIN

Aspirin is widely used as an anticoagulant because of its antiplatelet aggregation properties. As an eicosanoid, it also

has an anti-inflammatory effect. Whether ulcer healing was promoted by inhibiting platelet aggregation or by reducing inflammation has yet to be determined.¹

What is the evidence for the use of aspirin in the treatment of venous leg ulcers?

A randomized-controlled trial in 20 patients using compression, comparing daily oral enteric-coated aspirin 300 mg with placebo in 20 patients, found that after 4 months of treatment, 38% of the patients receiving aspirin compared to 0% of those receiving placebo had healed. Additionally, 52% of the aspirin-treated group showed significant reduction in ulcer size compared with 26% of placebo recipients ($p < 0.007$).^{8,52}

However, current guidelines suggest that results of a small single study is not enough evidence to make a recommendation.²¹

What is the evidence for the use of stanozolol in treating venous leg ulcers?

Stanozolol is an androgenic synthetic androgen with testosterone properties that is used in the treatment of hereditary angioedema and muscle building. Possessing fibrinolytic properties, for venous leg ulcers, it is thought stanozolol may be able to break down pericapillary fibrin cuffs because of these fibrinolytic properties, it has been effective in chronic and acute lipodermatosclerosis but no studies have demonstrated an increase in the rate of healing of ulcers within affected skin.¹

What is the evidence for phlebotonics in venous leg ulcer treatment?

There are several members in this drug group such as rutosides, hidrosmine, and diosmine, calcium dobesilate, centella asiatica, French maritime pine bark extract, aminafitone, grape seed extract, and horse chestnut seed extract. There is a suggestion of phlebotonics improving edema, although this is of uncertain clinical relevance.^{51,53}

A wide review of the efficacy of phlebotropic drugs have been published in a Cochrane Review. Evidence exists to show a reduction of edema in chronic venous disease; however, no superiority was demonstrated over compression in treatment of venous ulcers or in preventing venous ulcer recurrence. These findings may suggest edema reduction alone is insufficient to treat leg ulceration. This study analyzed different phlebotonic drugs without finding significant difference between each other. Further well-designed studies comparing different types of phlebotonics with compression in the setting of venous ulceration may give stronger evidence for its use.^{39,53}

What is the evidence for antitumor necrosis factor- α agents when treating venous leg ulcers?

As pentoxifylline has been shown to help heal venous ulcers even with a slight effect on tumor necrosis factor- α it has been suggested that other agents with tumor necrosis factor- α inhibition properties may have benefit in treatment of venous ulcers. Additionally, chronic wound fluid has been studied and local alterations in levels of proinflammatory cytokines and tumor necrosis factor alpha (TNFa) levels have been found compared to normal skin and acute wounds. Chronic wound fluid adversely affects young, rapidly proliferating fibroblasts such and that, which induces fibroblast senescence. Weinstein proposed that the mechanism of action of anti-TNF α agents is not only to blocks TNFa but to reduce the number of monocytes/macrophages thus, reducing TNFa levels and regulating key inflammatory cells.⁵⁴ Currently there are laboratory and pilot studies whose results suggest its potential use.^{16,55}

What is the evidence for isosorbide dinitrate in the treatment of venous leg ulcers?

Isosorbide dinitrate (ISDN) causes vasodilation in arterial and venous capillaries through nitric oxide (NO). A spray that contained ISDN was studied in a randomized double-blinded placebo controlled trial. Forty-five patients were treated with ISDN (2.5 mg) or placebo for 12 weeks daily plus continuous elastic support and leg elevation. Biopsies at the beginning of the study and 1 month later were taken. Fifteen patients received the drug and 30 patients received placebo. Patients who received ISDN treatment showed an improvement of 71.29% wound size reduction at 3 months compared to 54.35% of the patients treated with placebo ($P=.05$). The histopathologic improvements showed an increment in the number of hyperplastic capillaries from 1.2 to 1.6 in the ISDN-treated group and 0.8 to 1.0. However, hypertrophic capillaries in the ISDN-treated group were less (0.6- 0.8) than in the control group (1.0-1.6).⁵⁶

What is the evidence for honey in the treatment of venous leg ulcers?

Honey has been used for centuries in wound healing and there is literature that avails its properties: antibacterial, stimulation of cell growth cytokine release, etc, that may ultimately aid in healing.⁵⁷

Jull et al. in an open-label randomized trial randomized 368 patients to usual care or to calcium alginate dressings, impregnated with manuka honey (all participants were on compression), and were followed for 12 weeks.

One hundred and four ulcers (55.6%) healed in the treatment group and ninety ulcers (49.7%) healed in the control group. This difference was not significant and surprisingly increased frequency of infection was seen in the treatment group compared to the placebo group.⁵⁸

What is the evidence for using *calendula officinalis* when treating venous leg ulcers?

Calendula officinalis is a plant that is native to southern Europe. Calendula flowers are used in medicine either in infusions, tinctures, liquid extracts, creams or ointments, or in one of a number of skin and hair products available over-the-counter across the globe.⁵⁹

It has antimicrobial, analgesic, anti-inflammatory, and antioxidant properties and has been used in venous leg ulcers, burns, trophic ulcers, and skin lesions.⁶⁰

Duran et al. conducted a randomized-controlled trial in 34 venous leg ulcer patients receiving 7.5% Calendula ointment or saline dressings for 3 weeks and showed that wound area decreased by 42% in the Calendula group compared to 15% in the control group. The difference between the two groups was statistically significant ($P<0.05$).⁶¹

What is the evidence for pale sulfonated shale oil when treating venous leg ulcers?

A randomized, controlled, observer-blind, multicenter study compared pale sulfonated shale oil (PSSO) and compression versus compression and the PSSO vehicle.⁶² One hundred nineteen patients were of which 62 received PSSO and 57 received the vehicle. After treatment, ulcer size was significantly smaller in the PSSO group compared to the vehicle group $P=.0005$. Cumulative reduction in ulcer area was significantly greater in the PSSO group compared to the vehicle group ($P<.0001$). There was no difference in adverse events compared to the vehicle, neither was there difference in pain. Additionally, the new agent was safe and well tolerated. The proposed mechanism of action of PSSO is anti-inflammatory action and it has also shown antibacterial in vitro.

GROWTH FACTORS

During wound repair there is an orchestrated humoral and cellular response that is altered in chronic wounds. It has been found that growth factors levels are decreased in chronic wound fluid; it justifies studying growth factors as potential therapeutic options. The most promising growth factors that require clinical testing are vascular endothelial growth factor (VEGF), fibroblast growth factor (FGF), and granulocyte monocyte colony stimulating factor (GM-CSF). Platelet-derived growth factor (PDGF-BB) has

already been approved by the FDA for diabetic ulcers.^{16,63}

Granulocyte monocyte colony stimulating factor (GM-CSF) has been shown to be increased in the epidermis in wounded skin. It is particularly important during the inflammatory stage of wound healing, increasing the number of neutrophils, and enhancing their function at the wound site. In vitro studies have shown GM-CSF to increase keratinocyte proliferation and thus enhance reepithelialization. It has been suggested that GM-CSF works directly on the keratinocyte but also indirectly by up-regulating IL-6.⁶³

It has been reported that GM-CSF treatment is followed by VEGF transcription in the ulcer bed by different cell populations. This effect is associated with a higher number of proliferating keratinocytes at the wound edge, increased formation of granulation tissue and enhanced neovascularization. This effect is not significantly appreciated in wound fluid of acute wounds in healthy subjects.⁶⁴

What is the evidence for growth factors in the treatment of venous leg ulcers?

A phase I study in venous leg ulcers and periulcer injection of a replication incompetent adenoviral construct, expressing platelet-derived growth factor-beta (PDGF-beta), demonstrated the initial safety, feasibility, and biologic plausibility of using H5.020CMV.PDGF-beta to treat venous leg ulcer disease.⁶⁵

Several case reports and pilot studies have demonstrated that granulocyte-macrophage colony-stimulating factor (GM-CSF) administered locally promotes significant healing of venous ulcers. One clinical study that involved thirty-eight patients with venous ulcers were treated with topical rhu GM-CSF and compression dressing. Complete healing was observed in 47 of the 52 ulcers (90.4%). The average healing time was 19 weeks. No systemic or local side-effects from the therapy were observed. After 40 months, no reulceration of the healed ulcers was observed, but two patients developed new ulcers on the same leg.⁶⁶

Intralesional GM-CSF has been studied as well. A double-blind, randomized, placebo-controlled study which enrolled 60 patients with chronic venous leg ulcers, whom were treated with placebo or with 200 or 400 ug of granulocyte-macrophage colony-stimulating factor by perilesional injections of the drug in 4 weekly treatment episodes. The placebo group had 19% of ulcers healed at week 13, 200 ug of GMCSF had 57% healing and the 400 ug group had 61% healing.⁶⁷

What is the evidence for the use of zinc in the treatment of venous leg ulcers?

Zinc is an essential trace metal that is necessary for some enzymes and hormones to function. It also has anti-inflammatory effects on phagocytic cells. Zinc-deficient

individuals demonstrate slower wound healing and are more prone to infections and are thought that by treating zinc deficiency with 30 to 150 mg per day wound healing would improve.⁶⁸

Current guidelines state that adding zinc to patients without a deficient total body zinc reservoir will not improve healing of chronic wounds such as venous ulcers.²¹

A meta-analysis that involved diabetic foot ulcers and venous ulcers found seventy patients in four studies that compared oral zinc sulphate with placebo in people with venous ulcers and did not find a statistically significant difference between the two groups. These studies did not meet quality criteria for its results to be determinant, larger and well-designed studies will give more information regarding zinc supplementation in venous leg ulcer healing.⁶⁹

ANTIBIOTICS AND ANTISEPTICS

As an opening in the skin barrier, a venous ulcer is a potential entrance door for local and systemic infection, the use of topical and systemic antiseptics and antibiotics may appear to make sense when treating venous leg ulcers, but considerations regarding emerging resistant organisms suggest paying attention when including such an agent in the wound treatment scenario.

Some of the topical preparations that have been used in venous leg ulcers are cadexomer iodine, povidone iodine, peroxide-based preparations, ethacridine lactate, acetic acid, silver preparations and mupirocin.⁷⁰

What is the evidence for antibiotics and antiseptics in the treatment of venous leg ulcers?

Current guidelines state that systemically administered antibiotics do not effectively decrease bacterial levels in granulating wounds; however, topically applied antimicrobials can be effective and should be discontinued after the infection has cleared to minimize any possible cytotoxic effects because of the antimicrobial agent or emergence of bacterial resistance to the agent.²¹

As a result a recent Cochrane meta analysis showed that evidence does not support the use of systemic antibiotics to treat venous leg ulceration but found a statistically significant difference in group comparison in favor of the anti-helminthic levamisole when compared with placebo. This result may have been by chance due to the characteristics of the study. Systemic antibiotic therapy should be used in established cellulitis and or further extended infection. Results of this study support the use of cadexomer iodine as topical preparation.^{21,71}

What We Know

- Venous leg ulcers are the result of sustained ambulatory venous hypertension, which is caused by calf muscle pump failure most commonly caused by venous disease and valvular incompetence.
- The prevalence of venous ulcers increases with age and is higher among women. The estimated lifetime prevalence for leg ulceration in developed countries is 1%.
- Confirmation of the venous disease is desirable and color duplex ultrasound scanning is useful.
- Several compression modalities exist for treating and preventing the recurrence of venous ulceration, selection of a definite modality depends on a particular patient.
- Wound bed preparation is helpful to decrease the bacterial bioburden, remove debris and de vitalized tissue, stimulate healing and set the environment for dressings and adjuvants to work.
- Dressing choice would rely on cost-effectiveness and exudates management as well as patient tolerability. There is evidence of cadexomer iodine to increase healing rate compared to other dressings.
- Superficial venous surgery does not speed healing but prevents recurrence when added to compression.
- The use of bilayered artificial skin helps healing in venous leg ulcers.
- Limited evidence exists for NPWT in venous leg ulcer healing. It may be useful prior to or after a skin graft.
- Electromagnetic therapy may be useful in reducing the size of venous leg ulcers.
- Laser therapy and hyperbaric oxygen therapy do not have enough evidence to recommend their use in the treatment of venous leg ulcers.
- Pentoxyphilline is effective in promoting leg ulcer healing when used in with compression treatment.
- Micronized purified flavonoid fraction is helpful in long-standing and larger ulcers.
- Phlebotonics decrease leg edema but do not improve healing rate in venous leg ulcers.
- Promising therapies such as TNF α inhibitors are currently under investigation.
- Zinc supplements in patients without a deficient total body zinc reservoir will not improve healing of chronic wounds such as venous ulcers.
- The use of systemic antibiotics to treat noninfected venous leg ulceration has no effect in speeding healing.
- Isosorbide dinitrate showed statistically significant reduction compared to placebo in a small group of patients.
- Honey dressings compared with calcium alginate did not show statistical significant results in healing and increased the frequency of infection.
- Calendula officinalis versus saline showed reduction in wound area.
- Pale sulfonated shale oil decreased ulcer size in one study.

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Treatment of Hypertrophic and Keloid Scarring

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INTRODUCTION

In the developed world alone, over 100 million people acquire new scars every year and 11 million of these individuals go on to develop keloid scarring as a result.¹⁻⁷ Of the 4 million burn scar victims, 31-91% develops hypertrophy and in general, hypertrophic (HT) scarring occurs in 40% of individuals following surgery.^{1,5,7,8} After either accidental or elective dermal trauma, a complex healing process is initiated with the ultimate aim of wound closure.¹ The accompanying scar formation and continued development is governed by the nature of the inflammatory response initiated and has a tendency to be further exacerbated when the original injury reaches a critical depth of wounding.⁹⁻¹³ Skin scarring is not an aberrant or pathologic process, but normal healing activity being expedited in order to prevent life-threatening infection.^{13,14} Many mammalian embryonic studies have demonstrated that early gestation skin wounds can heal without scarring, but this ability is lost as fetal development progresses.^{14,15} Wound healing may result in a spectrum of scars, differing in quality and quantity between individuals. Indeed, variations in scar quality and consistency have been described within the same individual and even within the same lesion.^{1,16} Several scar types have been described, ranging from a fine line scar to atypical scars such as widespread scars, atrophic scars, HT scars and keloids (Figure 51-1 thru 53-4). Typically, HT scars appear red, raised and inflamed, but they can be defined by the characteristic that they stay within the boundaries of the original lesion and often regress spontaneously^{1,8} (Table 51-1). In contrast, keloid scars are distinguished by their raised irregular-shaped appearance and tough fibrous texture which characteristically spreads past the original margins of the wound and invades the surrounding normal tissue without penetrating below the dermal structure.¹ Keloid lesions are not harmful or life-threatening and typically grow from small nodular lumps at the site of a skin surface injury.¹⁷ They can vary in size from a few millimeters to the size of a small ball, or larger, and severe cases

appear reminiscent of neoplastic disease albeit benign.^{18,19} They do not regress spontaneously, but continue to grow with time and recur following surgical excision. Keloids histologically harbor thick hyalinizing nodular bundles of collagenous tissue which are typically absent in HT scars.²⁰ They are unique to humans and have a higher incidence rate in darkly pigmented skin such as in the African and Asian populations.²¹⁻²³ A strong genetic predisposition for keloid scarring has been suggested because of increased familial clustering, the prevalence in certain races and identical twins.^{24,25} However, keloid disease appears to be heterogeneous as both the dominant and recessive inheritance has been reported.²³ The condition may also be a cutaneous manifestation of an underlying fibroproliferative disorder and keloid-affected individuals, in contrast to HT, can exhibit an incidence of allergic responses.^{26,27} Both keloid and HT scars can occur at any site in the body, however, keloid scars are more prevalent and tend to have an increased severity in sites of increased tension or motion such as the chest and shoulder girdle, which is considered an 'activation' factor. Immune and hormonal changes, often during puberty increase scarring propensity and this can return in pregnancy. The growth pattern of keloid lesions is often lobular in an ear site (frequently post ear-piercing), butterfly shaped on the outer shoulder (after vaccination) or on the midchest (commonly after an acne spot).¹ Both scar types develop with the same prevalence in males and females, they typically present initially between 10-30 years of age and are less likely to occur in early years or later life.²⁸ It has been proposed that this occurs because of a combination of more traumatic events in the young with an increased dermal tension in younger skin.²³ Frequently, scars can remain within the boundary of the original lesion like HT lesions, but grow rapidly in size similar to keloid scarring – these have loosely been coined 'intermediate' scars²⁹ (Figure 51-5). Given the continuum of scar types, a well-defined distinction between these different scars does not exist.^{1,30} This reflects the broad variety of factors, which



FIGURE 51-1 An illustrated example of a flat stretched scar.

FIGURE 51-2 An illustrated example of a depressed scar.



FIGURE 51-3 An illustrated example of a hypertrophic scar.



FIGURE 51-4 An illustrated example of a keloid scar.

TABLE 51-1—Table of the Clinicopathologic Differences between Hypertrophic and Keloid Scars

Hypertrophic	Keloid
● Raised, linear, firm and generalized erythema	● Raised, lobulated, hard, and erythema at the periphery
● Develops soon after (within 3 months) time of dermal injury	● Often develops months (up to 1 year) after trauma/wound closure
● Occur at any anatomical site	● Occur in anatomical site patterns
● Growth remains within the margin or the original dermal injury	● Growth extends outside the margin of the original tissue and invades healthy tissue
● Often regresses spontaneously	● Does not normally regress
● Parallel orientated collagen type III	● Disorganized collagen type I and III
● No known associations with ethnicity, genetics and hormonal imbalance	● Are commonly associated with ethnicity, genetics and hormonal imbalance



FIGURE 51-5 An example of an intermediate raised dermal scar.

operate synergistically during the wound healing process on a genetic, physiologic and biochemical level.^{13,16,28,31}

As scars mature during the remodelling phase they often continue to express a wide variety of characteristics and symptoms which may regress or exacerbate.³² Such symptoms commonly reported with cutaneous scarring are hypertrophy, redness, pruritus, paraesthesia and pain.^{32–35}

Symptomatic provocation is more common in raised scarring and arises regardless of cause, size, or depth of the injury.^{34,36} It has been suggested that abnormalities associated with the small nerve function surrounding raised scars lead to a neuropathy effect with the outcome of pruritus and pain stimulation.³² Additionally, mast cells involved in the healing process contain mediators (including histamine and substance P³⁷). Raised scars have been shown to have higher levels of substance P nerve fiber density, greater substance P quantities and an increased number of mast cells.³³ Substance P is thought also to mediate pain via small unmyelinated C nerve fibers³⁸ and in raised scars may contribute to an exuberant neuroinflammatory response caused by a reduction in its regulatory (endopeptidase) enzyme.³⁹

Hence, scars possess both subjective and objective dimensions, therefore a thorough scar assessment should encompass both.⁴⁰ It is reported that all types of scarring can adversely affect cosmesis, function, psychological state, and growth.¹⁴ Subjectively many well-known tools are currently utilized such as the Manchester Scar Scale (MSS)^{41,42} (Figure 51-6) and additional questionnaires have been recently developed to incorporate the evaluation of ‘quality of life’ for scar sufferers.^{43–45} To the affected individual, unsatisfactory scars can represent a visual history of a traumatic event and serve as a ‘flash-back reminder.’ In addition, if an operation is involved, the

Visual Analogue Scale			
		Excellent	Poor
	A	Colour (cf. to surrounding skin)	
Lighter	□	Perfect	1
Or		Slight mismatch	2
Darker	□	Obvious mismatch	3
		Gross mismatch	4
	B	Matte (1)/ Shiny (2)	
	C	Contour	
		Flush with surrounding skin	1
		Slightly proud/ indented	2
		Hypertrophic	3
		Keloid	4
	D	Distortion	
		None	1
		Mild	2
		Moderate	3
		Severe	4
	E	Texture	
		Normal	1
		Just palpable	2
		Firm	3
		Hard	4

FIGURE 51-6 The Manchester Scar Scale.^{1,42}

TABLE 51-2—The Structured Scar Management Plan (As Practiced by the Senior Author)

1. Assess the Patient	<ul style="list-style-type: none"> ● History (including history of presenting condition, presence of other raised scars, past family history of keloid scarring, medical history, drug history, allergy) ● Examination (4-S/10-S Guide, Manchester Scar Scale, objective assessment of scar morphology) ● Investigations (consider USS, CT, MRI if indicated) ● Diagnosis (Differential diagnosis, scar type) ● Photograph (Pretreatment)
2. Counsel the Patient	<ul style="list-style-type: none"> ● Expectations ● Time course of Rx ● Compliance: Need for regular and long-term follow-up ● Psychosocial needs- ? referral
3. Appropriate Treatment	<ul style="list-style-type: none"> ● Leave alone (wait and watch! approach if scars are asymptomatic and non-progressive) ● Noninvasive (often first line of Rx but not always!) ● Invasive (choose appropriate option based on level of evidence or nature of scarring/symptoms/progression) <p>*Multi-disciplinary approach: Involve occupational therapy, physiotherapy, pain specialist, clinical psychologist if necessary.</p>
4. Regular Follow-up	<ul style="list-style-type: none"> ● History (Monitor changing symptoms) ● Examination (Monitor changing signs) ● Photograph (At every visit and post-treatment) ● Keep family physician informed of Rx & progress.

person's perception of the success of an operation can be negatively affected.⁴⁶ A focused clinical assessment is a prerequisite for the correct management strategy to be chosen and evaluated in abnormal scarring. A thorough initial structured assessment process (Table 51-2) should include a medical history, gender, ethnicity, age, the scar history (including age of onset, cause, progression and rate, previous home and clinical treatments, and recurrence) allergies, drug history, and psychosocial, family and fibrotic scar history. Following this, the clinical assessment should comprise the '10-S Guide to Clinical Assessment of Abnormal Skin Scars'³⁰ (Table 51-3); symptoms, severity, stigma, site, size, shape, shade, surface, surroundings and substance. Alternatively, the 4-S guide¹ can be used as a quick and brief clinical assessment in a busy clinic (Table 51-4). It is recommended that a standardized color photograph be taken as a reference point, especially for those with growing or recurrent lesions.^{30,47} In general, linear scar redness is considered to persist an average of seven months but often varies depending on existing pathogenic characteristics, time taken to wound closure, original wound depth and scar locality.^{1,9,48} While burn scar hypertrophy specifically has been noted to increase gradually between 2-6 months and most significantly from 6-12 months, then begins to regress and flatten at 18-24 months.^{3,49} The use of a skin substitute in the grafting process may also affect burn scar formation.^{49,50} Studies have reported the general prevalence of hypertrophic scarring in spontaneously healing wounds at 30% in dark-skinned individuals and 15% in the Caucasian population.^{4,5}

TABLE 51-3—The 10-S Guide to Clinical Assessment of Abnormal Skin Scars³⁰

Scar Guide	Range of Clinical Findings
1. Symptoms	Pruritus, pain, altered sensation, dryness
2. Severity	Disfigurement and functional impairment or disability (e.g., joint contracture)
3. Stigma	Psychological (e.g., lack of self esteem, depression), and social problems (e.g. unable to interact socially)
4. Site	High risk anatomic areas (sternum, deltoid) to low risk areas (e.g., legs, feet)
5. Size	Small (<3 cm), medium (3-5 cm), large (5-10 cm), giant (>10 cm)
6. Shape	Regular (geometrical design, e.g. ovoid) to irregular (no obvious geometry, invasive expansion into surrounding skin)
7. Shade	Color (hyperpigmented to hypopigmented scar) and erythema (matt or shiny)
8. Surface	Raised, flat or depressed contour
9. Surroundings	Distinct or indistinct margin
10. Substance	Scar texture and consistency: Soft, firm or hard

High numbers of these patients will receive scar modulation therapy. Numerous treatment modalities have been employed with varying degrees of success, and standardized criteria that define response or failure have not been established in every scar type.⁵¹ Currently

TABLE 51-4—The Quick 4-S Guide to Clinical Assessment of Abnormal Skin Scars¹

1. Site	Anatomic location of scar
2. Symptoms	Pain, itching, dryness etc
3. Severity	Of appearance/functional impairment
4. Stigma	Psychosocial impact on patient

abnormal skin scarring is often subject to an array of scar management modalities. These therapies can be administered in isolation, or, in combination, and are thereby termed as ‘monotherapy’ or ‘polytherapy’ treatment programs. Many raised scars do not respond satisfactorily to current treatments and the working evidence-base behind many treatment mechanisms is limited.⁵² A suitable management plan must always be carefully considered as attempts at some therapies can exacerbate the scarring already present, as keloids frequently recur in 50–80% of cases.^{18,28} The healthcare field is consistently being driven to supply safe and effective interventions, which provide the greatest quality care and value for money. Therefore, evidence-based medicine is key and requires the practitioner to integrate clinical knowledge and judgment with the best available evidence^{53,54}. There have been a number of large critical review papers,^{8,28,51,55–59} which provide recommended guidelines.⁶⁰ However, what constitutes the best evidence also requires the ability to identify, critique, and categorize the available literature by placing it into the ‘hierarchy of evidence’ with a ranked-order.⁵⁴ This ranking has been attempted previously for keloid scarring treatment only,⁶¹ but not incorporated keloid and HT lesions together. Therefore, although both types of scarring are in true-form separate entities, clinically these appear to overlap frequently.^{27,55,60,62} This chapter aims to identify primary clinical studies, which evaluate the management of HT and keloid scar treatments over the last 20 years, and to assign hierarchical levels of evidence to the therapeutic modalities assessed.

METHOD

A broad literature search was conducted to identify relevant clinical studies published in the last 20 years and indexed in the following databases: Medline, Cinahl, Embase, Scopus, Pubmed and Scirus (1990 – 2010). This included the keywords (applied individually and in a variety of combinations): “scar”, “keloid”, “treatment”, “hypertrophic”, “management”, “silicone”, “silicon”, “cryotherapy”, “cryosurgery”, “steroid”, “corticosteroid”, “injection”, “surgery”, “excision”, “laser”, “pulsed light”, “irradiation”, “radiation”, “radiotherapy”, “fluorouracil”, “interferon”, “verapamil”, “imiquimod”, “mitomycin”,

“pressure”, “compression”, “paper tape” and “dressing”. Only English language publications of clinical studies and case reports for the prevention or management of keloid or hypertrophic scar were included. The bibliographies of relevant literature review articles obtained were examined for further significant published evidence, until no additional study papers could be established.

The full-text articles were grouped into principal therapeutic management categories, and then sub-classified into monotherapy and polytherapy groups. Where a single study compared a monotherapy to a polytherapy, the article was listed in both subgroups. Examination of the methodological quality of each study was undertaken in order to assign a level of evidence (LOE) for each clinical trial⁶¹ adapted from the Oxford Centre of Evidence-based Medicine.⁶³

In order to establish the LOE, study methodologies were inspected for their overall study design (including retrospective or prospective analysis), the sample size, the randomization and allocation of concealment technique, the outcome parameters and standardized tools selected, assessor blinding, placebo controls and total duration of the follow-up. The randomized-controlled trial (RCT) is considered the gold standard of the ‘hierarchy of evidence’ by most clinicians.⁶⁴ This encompasses a double-blinded, randomly allocated and placebo or active comparator designed study.⁵⁵ Studies were downgraded if these qualities were absent according to Table 51-5. The overall conclusive findings were also reviewed to determine the statistically significant positive or negative therapeutic outcomes or the documented effectiveness levels (e.g., for comparative studies) in each modality evaluated.

TABLE 51-5—Levels of Evidence

Level	Study Type
LOE-1	Systematic review (SR) of RCTs High quality RCT
LOE-2	Low quality RCT SR of cohort studies Cohort study/non-randomized-controlled trial
LOE-3	SR of case-control studies Case-control study
LOE-4	Case-series Low-quality cohort study/ Non-randomized controlled trial Low-quality case-control study
LOE-5	Case reports Expert opinion without critical appraisal/based on physiology/bench research/first principles'

(Adapted from the Oxford Centre for Evidence-Based Medicine)^{61,63}

RESULTS

A total of 173 primary studies were determined using the search strategy described here. These were divided into 17% RCTs, 1% systematic reviews, 9% case-control studies, 15% comparative studies, 49% case-series, and 9% case reports (Table 51-6). Individual results for each treatment modality are discussed separately and are listed in Tables 51-7 thru 51-19.

SILICONE-BASED THERAPY

Since the early 1980s, silicone gel (SG) has been used widely in the management of HT and keloid scars.^{60,65,66} Silicone products are available in various forms with a range of compositions, durability, and adhesive properties. To date most clinical trials have involved the assessment of pure adherent silicone gel sheeting (SGS).⁶⁰ However, other forms of liquid SG or oil,⁶⁷⁻⁷⁴ silicone cream (SC)^{75,76}, nonadherent silicone gel cushion (SGC)^{77,78} and SG with added vitamin E⁷⁹ have been trialled.

Silicone gel sheeting is a soft, semiocclusive dressing, made from medical grade silicone (dimethylsiloxane cross-linked polymer) reinforced with a silicone membrane backing⁶¹. All forms of SG are topically applied agents, which are noninvasive, easy to use, painless, convenient, and present at a relatively low-cost therapeutic option.^{80,81} While this modality is widely used for the management and prevention of pathogenic scarring, the exact mechanism continues to remain elusive.^{81,82} However, the main postulated occlusive effect of SGS is thought to lead to a reduction in the transepidermal water loss, establishing

homeostasis in the epidermal barrier layer and leading to a possible advanced state of wound repair.^{81,83} SGS or silicone in its various forms is frequently used as a monotherapy in raised scarring, especially in burn hypertrophic lesions. It is also combined frequently with intralesional steroid (ILS) injections,^{72,84-87} cryosurgery (CS),⁷² laser,⁸⁸⁻⁹⁰ pressure therapy,^{85,86,91} and after surgical excision^{84-86,90,92} for problematic keloid lesions. SG products are generally well tolerated by HT and keloid scar patients.^{67,79,93-95} SGS is often required to be worn for 10-24 hours^{77,79,96,97} each day and for several months.^{94,98} Nevertheless, studies frequently report a small percentage of side-effect in treated cases including the presence of a rash, persistent pruritus, skin maceration, or breakdown.⁹⁹⁻¹⁰² These minor problems quickly resolve upon removal of the silicone and may be avoided if patients are correctly instructed on the methods of daily cleaning and reapplication to prevent bacterial irritations.^{96,99,103} Therefore, patient vigilance and compliance is essentially important, along with an enhanced education program from the clinician.^{27,104}

A number of randomized and nonrandomized trials have demonstrated the effectiveness of silicone monotherapy to soften scars, reduce the height, erythema, diminishing symptoms such as pain and pruritus, improve the overall pliability and contracture rate associated with HT,^{67-73,77,79,88,94-99,102,105-109} and keloid^{68,69,72,77,79,88,96,105,110} scars (Table 51-7). Additionally, silicone can be used prophylactically to prevent abnormal scar development.^{67,68,70,94,95,102,109,111,112} Five RCTs (LOE-2)^{94-96,102,113} compared SGS to untreated control scars. In De Oliveria's⁹⁶ study, 41 (HT and keloid) scars in 26 patients were trialled

(text continues on page 775)

TABLE 51-6—Summary table of Levels of Evidence per Treatment Modality of Raised Dermal Scars (Hypertrophic and Keloid)

Treatment Modality	LOE-2 (Monotherapy / Polytherapy)	LOE-3 (Monotherapy / Polytherapy)	LOE-4 (Monotherapy / Polytherapy)	LOE-5 (Monotherapy / Polytherapy)
Silicone	13/3	4/0	14/7	0/3
Cryosurgery	1/0	0/0	9/4	1/0
Steroids	7/4	1/0	7/24	0/4
Excision	1/3	0/0	4/50	1/6
Lasers	6/1	5/0	11/5	2/1
Radiotherapy	1/1	0/0	4/27	0/2
5-Fluorouracil	1/3	0/0	4/4	0/2
Interferon	1/1	0/0	4/3	1/0
Verapamil	0/0	0/0	1/3	0/0
Imiquimod	0/0	0/0	0/4	0/1
Mitomycin C	0/0	0/0	0/4	0/0
Pressure	1/2	0/0	0/10	0/2
Other	7/3	0/0	9/5	1/2

TABLE 51-7—Monotherapy and Polytherapy Published Clinical Trials: Silicone Treatment Modality

Silicone	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
O'Brien ¹⁰⁵	2	Systematic review	RCT & controlled trials evaluating the effectiveness of SGs	HT & K	15 trials involving 615 people age 2-81 years were included	Reduction in scar parameters & symptoms	Various SGs & non-SGs (adhesive and nonadhesive) to other therapies or controls	n/a	+weak benefit for SGs as a preventative strategy (NS)	Treatment trials for SGs use in K and HT scarring are of generally poor quality and highly susceptible to bias. Evidence is weak for the benefit of SGs as a preventive strategy for abnormal scarring in high-risk individuals. Overall the poor quality research leaves a great deal of uncertainty.
De Oliveira ⁶⁶	2	RCT	SGS vs placebo sheet vs untreated control	HT & K	26 patients (7 ethnicity or skin type) with 41 HT or K scars, excluded if radiation or steroid therapy in previous 12 months, or lesion <3 months old	Scar size, coloured, induration & symptoms	Sheet: 24 hrs/day	4.5 months (prospective)	+SGS +placebo sheet	Significant reduction in parameters for silicone and control sheet groups compared to the control scars. No significant difference identified between silicone and control sheet groups.
Chan ⁶⁷	2	RCT	SG vs placebo gel	HT	50 patients (Asian ethnicities) with 14 day old standardized sternotomy wounds, excluded if infection or allergy to SG	Scar pigmentation, vascularity, pliability, height & symptoms	Gel: 2 x day application	2.5 months (prospective)	+SG	Significant reduction in all scar parameters for the SG scar areas. SG is effective in the prevention of HT scar development in sternotomy wounds.
Wittenberg ¹¹³	2	RCT	SGS vs PDL vs untreated control	HT	20 patients (Fitzpatrick skin type I-IV) with a linear HT scars ≥ 8cm long, excluded if received scar treatment in previous 2 months,	Scar blood flow, pliability, volume, symptoms & histologic biopsy assessment	SGS: ≥ 12 hrs/day, PDL: 4 treatments at 8 week intervals	10 months (prospective)	- SGS (NS) - PDL (NS)	Overall significant reduction in blood flow, volume and pruritus was recorded during the monitored phase in all scar regions. There was no difference in the improvement in scars sections treated with SGS or PDL compared to control sections.

(Continued)

TABLE 51-7—Monotherapy and Polytherapy Published Clinical Trials: Silicone Treatment Modality (Continued)

Silicone	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Majan ⁹⁴	2	RCT	SGS vs untreated control	HT	11 patients (7 ethnicity or skin type) with postoperative scars, excluded if known allergy to SGS, keloid scarring or underlying serious pathology	Scar pigmentation, height, pliability & vascularity, symptoms & overall scar appearance	SGS: 23 hrs/day	12 months (prospective)	+SGS (NS)	Results suggest the SGS group experienced greater and more rapid improvements compared to the control group.
Momeni ⁹⁷	2	RCT	SGS vs placebo sheet	HT	38 patients (7 ethnicity or skin type) HT burn scars, excluded if wound infection, open wound or sensitivity to SGS	Scar pigmentation, vascularity, pliability & symptoms	Sheet: 12-24 hrs/day	4 months (prospective)	+SGS	All scar parameters were significantly reduced in the SGS group in comparison to the control region after 4 months, except pain. For HT burn scars, SGS is an effective treatment.
Palmieri ⁷⁹	2	RCT	SGS vs SGC with added vitamin E	HT & K	80 patients (7 ethnicity or skin type) with HT and keloid scars, no exclusion criteria stated	Scar symptom, color, size & cosmetic appearance	Sheet: 10 hrs/night	2 months (prospective)	+SGC with vitamin E (NS)	SGC with added vitamin E scored better than simple SGS at both 1 and 2 month periods studied
Berman ⁷⁷	2	RCT	SGC vs SGS	HT & K	32 patients (7 ethnicity or skin type) with HT or K scars \geq 7 months old, no exclusion criteria stated	Scar size, volume, symptoms, color & induration	SGC/SGS: \geq 10 hrs/day	4 months (prospective)	+SGC (NS) +SGS (NS)	SGC and SGS are both effective treatments of K and HT scars, although no statistically significant results exist between the groups.
De Giorgi ⁶⁸	2	RCT	SG vs placebo control	HT & K	110 patients (Fitzpatrick skin type I-IV) with standardized surgical wounds and management, excluded dermatofibromas, sebaceous cysts and inflammatory cutaneous lesions	Scar vascularity, sensory stimulation & symptoms	Gel: 2 times/day	8 months (prospective)	+SG (NS)	SG reduced the formation of K and HT scars, along with improving the signs and symptoms associated with the healing process but not significantly.

Ahn ¹⁰²	2	RCT	SGS vs untreated control	HT	48 patients (7 ethnicity or skin type) with new wounds or HT scars, no exclusion criteria stated	Scar elasticity & volume	SGS: ≥12 hrs/day	6 months (prospective)	+SGS	New wound scars significantly reduce in volume in the SGS group compared to the controls. Established HT scars saw a significant improvement in elasticity over the control group.
Gold ⁹⁵	2	RCT	SGS vs untreated control	HT	96 patients (7 ethnicity or skin type) with low (n=50) and high (n=46) risk history of abnormal scarring, no exclusion criteria stated	Scar symptoms, embarrassment, color, height, texture & function	SGS: ≥12 hrs/day	6 months (prospective)	+SGS	Statistically significant reduced incidence of abnormal scarring in the high-risk patient group using SGS. There was no added benefit from additional silicone therapy in the low-risk group.
Sproat ¹⁰⁶	2	RCT	SGS vs ILS	HT	14 patients (7 ethnicity or skin type) with sternal scars, no exclusion criteria stated	Scar size, height, color & symptoms	SGS: 12 hrs/day, 12 weeks ILS (TA 40 mg/ml); 1 dose	3 months (prospective)	+SGS (NS)	SGS provided improved signs and symptoms more quickly than ILS.
Wigger-Alberti ¹⁰⁷	2	RCT	SGS vs polyurethane dressing	HT	60 patients (7 ethnicity or skin type) with HT scars ≥60 mm long, extensive exclusion criteria including K scarring and other treatments in the last 2 months	Scar overall appearance, color, matte/shiny, contour, distortion & texture	SGS/dressing: 23-24 hrs/day for 3 months to half of scar	3 months (prospective)	+polyurethane dressing > +SGS	Both regimes demonstrated a significant reduction in the clinical HT scar signs over 3 months. However, the polyurethane dressing was significantly better at reducing the clinical signs at 4 and 8-week reviews and was tolerated more than the SGs.
Polytherapy										
Sawada ⁷⁵	2	RCT	SC with light dressing vs SC with occlusive dressing vs placebo with occlusive dressing	HT & K	47 patients (7 ethnicity or skin type) with HT or K scars, excluded if infected or ulcerated scars	Scar redness, elevation, hardness, itching & symptoms	Cream: 1-2 times/day	3-5 months (prospective)	+SC with occlusive dressing > SC with light dressing	Statistically significant improvement in the SC and occlusive dressing group compared to the SC and light dressing group, with an improvement in redness, tenderness, itching and hardness recorded.

(Continued)

TABLE 51-7—Monotherapy and Polytherapy Published Clinical Trials: Silicone Treatment Modality (Continued)

Silicone	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Harte ⁹¹	2	RCT	Pressure therapy & SGS vs pressure therapy	HT	22 Caucasian patients with HT burn scars, excluded other scar types, presence of an infection or skin condition	Scar height, vascularity, pliability & pigmentation	Pressure therapy: pressure garment, SGS: applied under the garment for 23 hrs/day	6 months (prospective)	Pressure therapy & SGS = pressure therapy alone	No significant differences were established at 12 or 24 weeks between the two treatment groups, however both groups showed a general decrease in their group scar scores. Evidence here is inconclusive and a larger scale RCT is required.
Li-Tsang ¹²⁰	2	RCT	SGS & massage vs massage	HT	45 patients (Chinese ethnicity) with post-traumatic HT scars, no exclusion criteria stated	Scar thickness, pigmentation, height, vascularity, pliability & color	SGS: 24 hrs/day Massage: 15 mins/day for 6 months	6 months (prospective)	+SGS & massage > massage	Significant reductions in scar thickness at 2 and 6 months were noted in the SGS and massage group. Symptoms, pliability and pigmentation also improved with SGS and massage therapy.

RCT, randomized controlled trial; NS, not significant, +, positive; –, negative; SG, silicone gel; SGS, silicone gel sheet; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; 2, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; IL, intralesional steroid; IL, intrallesional; Exc, excision; ILExc, intralesional excision; ELExc, extrallesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetone; BM, betamethasone sodium phosphate.

to compare SGS with a nonsilicone occlusive dressing (if the patient had two scars present) and an untreated control (if the patient had 3 scars). The SGS was applied for 24 hours a day and nonvalidated measurements of scar size, induration, color, and patient-reported symptoms were recorded with intracutaneous pressure. There was no significant difference observed between the two treatment groups, but both treatments significantly improved parameters in comparison to the control scars. However, the randomization method was not stated, blinding occurred for only one outcome measure, a limited follow-up was completed, and both scar types were analyzed together. Ahn¹⁰² completed a RCT of 48 patients with new wounds or existing HT scars and utilized adjacent or mirror image scars on the same patient as a control. SGS was worn for a minimum of 12 hours a day and patients were followed up to 6 months. Scar elasticity using an elastometer and volume were the only outcomes monitored. No details of the randomization or blinding were reported and 10 patients were lost to follow-up. Significant improvements in existing HT scar elasticity were reported and new wounds significantly reduced in volume compared to controls.

Another HT scar RCT⁹⁵ focused on subgrouping participants based on the individual history of 96 patients with a high or low risk for abnormal scarring postsurgery. SGS was compared to a control routine postoperative care group. The patient and unblinded clinician observed scar changes using a nonvalidated linear score with scaled photographic analysis. A marginal improvement was observed in the high-risk group and a significant difference was obtained in those patients undergoing scar revision surgery. There was no added benefit from additional silicone therapy in the low-risk group. A small RCT⁹⁴ of 11 patients trialed SGS on 6 postoperative scars for 23 hours a day for a maximum 1 week, while the 5 postoperative controls had no treatment. A randomization sequence was completed and scars were evaluated using the Vancouver Scar Scale (VSS),¹¹⁴ along with rating symptomatic changes. The SGS treatment group experienced larger and more rapid improvements compared to the control group, with only one patient lost at the 12 months review point.

Alternatively, Wittenburg and colleagues¹¹³ compared SGS with PDL and untreated controls in 21 patients with linear scars. They found no difference in scar volume, erythema, or symptoms between treated and untreated regions. The authors' methodology consisted of computer randomization and assessor blinding coupled with a range of quantitative objective measures and 10 month monitoring. Hence, these added components may account for their contradictory results. Seven other RCTs (LOE-2)^{67,68,77,79,97,106,107} evaluated SG products against other treatment modalities or placebo therapies. Chan⁶⁷ administered a semi-liquid SG or a gel control to 100 14-day-old sternal scars in 50 patients. After 3 months, statistically significant improvements in all VSS parameters were recorded by a blinded assessor. A similar comparative

study⁶⁸ in two separate patient groups (i.e., treatment and control), with a follow-up period of 8 months demonstrated a reduced formation of both HT and keloid scars and improved symptom control. Two studies^{97,107} compared SGS to a placebo occlusive sheet. Momeni⁹⁷ completed a randomized and double-blinded trial of 38 HT burn scars divided into two separate halves. After 4 months, all VSS parameters except pain were significantly reduced compared to the placebo control sheet. Alternatively, 60 patients with HT scars received similar randomized treatment for 3 months and objective monitoring using a modified version of the MSS,⁴² quantitative chromometry and a nonstandardized patient questionnaire. The authors¹⁰⁷ found the polyurethane dressing to be significantly more effective than SGS. The variability of results from SGS versus occlusive dressing studies and the evidence against silicone penetration into the scar or stratum corneum^{115,116} pose a questionability of the requirements of silicone as an active component and positive requirement in these constructs.^{92,96} Berman⁷⁷ investigated SGS compared to a nonadherent SGC, a product reported to induce greater negative static-electric charges. However, after 16 weeks no statistically significant differences were determined, hence challenging the adherent occlusion to induce hydration theory. Additionally, when 80 patients were randomized to receive SGS alone or SGC plates coated with vitamin E and taped in place for 10 hours, the SGC with vitamin E proved more effective.⁷⁹ Nonvalidated outcome assessments, the limited follow-up period and lack of randomization detail do conversely weaken the methodology. In another study, Sproat¹⁰⁶ compared 14 patients with HT sternotomy scars receiving SGS for 12 hours a day for 12 weeks or a single dose of ILS. After 3 months, the blinded assessors and patients determined greater benefit to the scars treated with SGS.

Four case-controlled studies determined LOE-3, compared various types of SGS to untreated control scars^{69,99,108,109} and additionally to liquid SG.⁶⁹ Three studies^{69,108,109} involving a combined 92 patients reported statistically significant difference in outcomes treated with SGS. The participants treated with liquid SG, or liquid SG and SGS described a greater improvement than SGS alone.⁶⁹ Alternatively, Niessen⁹⁹ evaluated occlusive SG versus SGS compared to routine treatment in 155 breast reduction patients. One hundred and twenty-nine patients were available at the 1-year point for scar size measurements and objective device measurements of color, depth, and blood flow. No keloid scars were observed. Neither SG nor SGS prevented HT scar formation and in contrast to other studies, the silicone-treated groups fared worse and developed significantly more hypertrophy than the control group. The control group did, however, receive routine paper-taping and the authors suggested the SGS intervention may have been initiated too soon, as treatment started on day 3 postoperatively.

The remaining studies were case-control studies,^{88,110} low-quality non-randomized comparative studies^{70–73,98,117} and case-series^{74,78,111,112,118,119} comprising level 4 evidence. All studies concluded positively in light of the benefits of silicone-based therapy, except in three cases.^{72,110,117} Additionally, a single meta-analysis has been completed for the Cochrane review by O'Brien.¹⁰⁵ This includes 13 controlled studies of 559 patients and found that SGS reduced the incidence of HT scarring in individuals with a high propensity to develop the condition. A significant reduction in scar thickness and color was also determined after SGS therapy, but results were highly susceptible to bias.

Silicone therapy is frequently combined with other adjuvant treatments (see Table 51-7 and its electronic version). Three RCTs (LOE-2)^{75,91,120} exist to compare the efficacy of silicone-based products in combination with other therapeutic modalities. SC with a combined occlusive dressing was statistically more effective than SC with a light dressing, or a placebo cream and occlusive dressing.⁷⁵ Results were recorded using a nonvalidated assessment and no details of the blinding or randomization were documented however. SGS has also been trialled in combination with deep massage for HT scars and proved an effective combination therapy to significantly reduce scar thickness and improve scar color as measured using standardized spectrophotometer and ultrasound devices.¹²⁰ Harte⁹¹ combined SGS with pressure therapy for a small sample study of 22 patients and found no significant difference in outcome compared to pressure therapy alone. Other combination therapy studies were non-randomized comparative trials^{72,88,92} or case-series^{76,84–87,89,90} of level 4 evidence and often involving some form of removal procedure, especially those studies encompassing keloid lesions.

CRYOSURGERY

Cryosurgery (CS) can be used as a monotherapy or in combination with a range of other therapies to treat in particular recurrent or difficult keloid lesions^{27,121,122} (Table 51-8 and its online version). Contact probes,^{121,123–125} sprays^{122,126} and intralesional CS (ILCS)^{127–130} needles can be used to apply the modality direct to the scar tissue. Liquid nitrogen is the most frequently used agent to freeze problematic HT or keloid lesions. Scar flattening is achieved through the process of selected tissue necrosis because of an induced cell and microvascular damage.^{103,125} This has been shown to positively affect collagen fiber architecture.¹²⁸ Interestingly, pathogenic-raised scarring does not occur post ‘frostbite’, therefore it is postulated that the fibroblasts may respond differently to the proinflammatory signals present.²⁷ Repeated CS sessions appear to have a beneficial effect on the outcome of HT and keloid scars and prevent relapses.^{125,130–132} CS is a success in 28–100%^{121,126,131,133} of cases with no reoccurrences reported at up to 6 years in

some studies.^{131,134} Younger patients,¹²⁵ with younger¹²⁸ or smaller¹³³ scars respond better to CS. However, there is a high drop-out rate for treatment because of the pain experienced and time taken for healing.^{103,135} Every 2–6 weeks the scar site should be assessed and the lesion subjected to 20–30 second thaw cycles (2.5 minutes in some cases),¹²¹ repeated 1–12 times in total dependent on overall lesion size.^{72,121,123,125,128,129} During the freezing process and immediately after treatment pain can be experienced. Hypopigmentation is a common side-effect of the treatment along with atrophy.¹³⁴ Rare incidences of auricular cartilage damage have also been reported.¹⁰³

One small double-blinded RCT (LOE-2)¹²³ of 11 patients compares CS to ILS injections and untreated controls in acne keloid scars. Patients received randomized treatment (n=1–3) over an 8-week period by an independent physician with an additional 8 weeks of follow-up. A spot freeze technique was applied, this allows the ice-ball to reach the outer limits of the scar under treatment and includes a margin of normal tissue.¹²³ The same observer evaluated palpability via a nonvalidated method and further clinical examination was completed using standardized length, depth, and blood flowmetry devices. Both treatments significantly improved height and palpability, with vascular lesions responding better to CS especially. CS was significantly more effective than ILS and back scars had a better result than chest lesions. A single non-randomized comparative study conducted by Yospovitch¹²² provided positive level 4 evidence for significant improvements using CS in conjunction with ILS, over CS or ILS alone. A spray freeze technique was employed from a distance of 1 cm continuously for 30 seconds. 10 patients were monitored for 10 months in total (8 months post-treatment) and although clinical evaluation was performed by the same observer, no blinding was described, except photographic ratings. A further 9 level 4 case-series studies, mainly evaluating CS with keloid scarring have demonstrated the positive benefit of this therapeutic modality.^{125–131,134} Four of these studies^{127–130} employed the method of ILCS, utilizing a probe with a sharp tip to penetrate dense HT or keloid scar tissue. One level 5 case report further affirmed the use of CS.¹²⁴ In addition, 4 (LOE-4) polytherapy trials combining CS with ILS,^{121,122,133} and ILS and SG⁷² have also proved positive with statistically significant results achieved in 2 studies.^{72,122}

STEROIDS

Intralesional injections of corticosteroids are considered the standard first line treatment for keloid scars and a secondary treatment for HT scars.^{65,136} Intralesional steroids (ILS) can also be administered as an adjunct therapy to reduce recurrence after various excision techniques.¹⁰³ A range of steroid preparations are available for intralesional injection, including hydrocortisone acetate, methylprednisolone

TABLE 51-8—Monotherapy and Polytherapy Published Clinical Trials: Cryotherapy Treatment Modality

Cryotherapy	Study Design LOE	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Monotherapy</i>									
Layton ¹²³	2	RCT	CS vs ILS vs untreated control	K	11 patients (?ethnicity or skin type) with multiple acne K scars, no exclusion criteria stated	Scar height, depth, blood flow & pliability	CS & ILS (TA 5 mg/mL):?1-3 treatments	4 months (prospective)	+CS >+ILS

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; IL, intrallesional steroid; IL, intralesional; Exc, excision; ELExc, extralesional excision; ELExc, extralesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetone; BM, betamethasone sodium phosphate.

acetate (MP), dexamethasone, betamethasone sodium phosphate (BM) and the most popular triamcinolone acetonide (TA). Injection of corticosteroids leads to the regression of keloid and HT scars by attenuating the inflammatory process, altering collagen gene expression, inhibiting collagen and glycosaminoglycan synthesis.¹³⁷⁻¹³⁹ Steroid-induced suppression of vascular endothelial growth factor may also further prevent fibroblast proliferation, promote fibroblast degeneration, and inhibit growth.^{28,140-142} Ultrastructural changes can also occur in keloid scars post-treatment to enhance collagen bundles and alter characteristic collagen nodules.¹⁴² Overall, the exact mechanism by which ILS aids scar size reduction and prevents reoccurrence is not fully understood. Some scars become resistant to ILS therapy when treated with hydrocortisone, this may be caused by the altered efficacy of some compounds on keloid fibroblasts¹⁴³.

Triamcinolone acetonide can be used at a combination of doses (1-40 mg/mL),¹⁴⁴⁻¹⁴⁸ and may be used in combination with lidocaine to reduce the pain from intralésional injections, especially in tender lesions.^{106,133,149} A needle or Dermo-Jet-injector can be used to administer the drug.^{28,137,146,150} Frequently, a series of injections are required for a satisfactory outcome, and this may occur every 1-4 weeks^{110,122,146} for 1-16 months.^{121,151,152} Response rates are highly variable, figures usually range from 50-100% and reoccurrence rates from 6-50%, but when ILS is combined with some adjuvant therapies such as a surgical excision, 'cure' rates can reach 80%.^{147,153-155} Topical steroid ointments are also available and have demonstrated some success.¹⁵⁶

Not only are steroid injections painful but they are also associated with a variety of side-effects: adverse hypopigmentation, telangiectasia, and skin atrophy was observed in 50-63% of tissue receiving ILS alone.^{65,145} Hypopigmentation often continues for years post ILS and is more highly visible in darker pigmented skin.^{8,57} Early administration of ILS postsurgical excision can also lead to wound dehiscence¹⁰³. Therefore, it has been suggested that sutures should remain in situ for an increased time if this adjuvant therapy is planned.^{85,157,158}

Seven RCTs (LOE-2, Table 51-9 and its electronic version)^{106,123,144-147,150} compare the use of ILS alone with various other treatments. Berman¹⁴⁴ conducted a study involving 20 patients comparing ILS with tumor necrosis factor (TNF)-a in keloid scars over a year old and ≤2cm in length. Equal study groups (n=10) received 20 mg/mL TA or 25 mg/mL etanercept intralesionally at baseline and 4 weeks later after an undisclosed randomization process. A visual analogue scale (VAS) was used by the clinician and patient to rate tolerability (erythema, pain and tenderness) and efficacy (cosmesis, pigmentation, satisfaction and pruritus). Induration, volume, and scar size were also assessed using various devices. Although the author-reported scar evaluations were blinded, it is unclear how this was achieved exactly, because assessments were completed by the study investigator. No statistically

significant differences were calculated from baseline levels over the short study period of 2 months for either treatment group or between treatment groups. TA did however, improve 11/12 parameters in comparison to etanercept which only proved effective on 5/12.

Another RCT¹⁴⁶ examined the potential benefit of combining ILS with 5-fluorouracil (5-FU) via a double-blinded parallel group trial. Over a 3 month period, 40 patients received weekly injections TA (40 mg/mL) or TA and 5-FU (50 mg/mL) for a total of eight treatments. Overall, seven drop-outs were reported between the groups (n=4 in ILS, n=3 in ILS and 5-FU). After 12 weeks, significant parameter improvements were seen in the ILS and 5-FU treatment arm compared to ILS alone. Patients reported a statistically significant overall scar improvement after combined therapy, whereas the trained observer response was not significantly beneficial. A computer-generated randomization and an external assessor were incorporated into the study design; however, a nonvalidated linear 5-point scale was used to measure erythema, induration, pruritus, and overall improvement.

These results echo a similar study¹⁵⁰ by the same group, which observed that ILS and 5-FU administered weekly for 2 months was statistically more effective than ILS alone. Nevertheless, the TA dose used was 25% lower in this study (TA, 10 mg/mL) and only a single-blinded design was presented. When an additional study arm here incorporated pulsed-dye laser (PDL) with ILS and 5-FU, additional significant improvements in itch and erythema were recorded, which yielded both patient and external observer statistical benefits. Other authors¹⁴⁵ determined that the addition of 5-FU does not increase the efficacy of ILS (TA 20 mg/mL) as a treatment in keloid or HT scar patients. This study divided long sternotomy scars into five sections with all 4-study treatment arms (PDL, ILS, 5-FU, ILS and 5-FU) randomized to different tissue sites along the length of the lesion. A 1 cm untreated barrier was marked-out between regions and one control site separated for further comparison. Treatment patterns (i.e., intervals and number of treatments) varied widely between the intralésional therapy groups. Outcome measures were largely standardized, validated, and parameter-specific quantitative instruments, with no assessor blinding described. Overall, all treated segments improved statistically, but no significant difference was determined between the groups. However, intralésional therapies resulted in a faster resolution than PDL. Although a small study (n=10), all patients received treatment into the same scar and it is assumed all were followed-up to the 8 months point as no drop-outs are recorded.

One RCT¹⁴⁷ compared 100 scars (n=58 keloid and n=42 HT) in 65 patients receiving ILS alone, β-radiation (RXT) alone, excision with β-RXT against excision with pre- and postoperative β-RXT. Patients were regularly followed-up for nearly 10 years. The ILS was administered according to the lesion surface area (1-2 cm², 20-40 mg; 20-6 cm², 40-80 mg;

(text continued on page 782)

TABLE 51-9—Monotherapy and Polytherapy Steroid Treatment Modality Published Clinical Trials

Steroids	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
Berman ¹⁴⁴	2	RCT	ILS vs TNF- α	K	20 patients (2ethnicity or skin type) with K scars ≥ 1 year old, ≤ 2 cm in length, extensive exclusion criteria including prior scar treatment in last 6 weeks	Scar erythema, symptoms, pigmentation, induration, volume & overall appearance	ILS (TA 20 mg/mL) or TNF- α : 2 treatments at 0 and 4 weeks	2 months (prospective)	+ILS (NS) +TNF- α	Both treatments improved several scar parameters at week 8, with ILS performing better than TNF- α although not significantly different compared to baseline. No statistical difference was apparent between groups, however TNF- α significantly reduced pruritus.
Sproat ¹⁰⁶	2	RCT	SGS vs ILS	HT	14 patients (2ethnicity or skin type) with sternal scars, no exclusion criteria stated	Scar size, height, color & symptoms	SGS:12 hrs/day, 12 weeks (TA 40 mg/mL); 1 dose	3 months	+SGS (NS)	SGS provided improved signs and symptoms more quickly than ILS.
Manuskiatti ¹⁴⁵	2	RCT	PDL vs ILS vs 5-FU vs ILS & 5-FU vs untreated control	HT & K	10 patients (Fitzpatrick skin type I-IV) with HT and K sternotomy scars, ≥ 6 months old, excluded if previously treated	Scar height, erythema, pliability, overall scar appearance & histology	PDL/ILS (TA 20 mg/mL); 6 treatments, 4 week intervals 5-FU (50 mg/mL); 10 treatments, every 2-4 weeks ILS (TA 1 mg/mL) & 5-FU (45 mg/mL); 10 treatments, every 2-4 weeks	≤ 8 months (prospective)	+PDL +ILS +5FU +ILS & 5-FU	Clinically and statistically all scars improved after ILS, ILS & 5-FU, 5-FU and PDL comparably. ILS, ILS & 5-FU and 5-FU alone resulted in faster resolution and better scar induration than the PDL treatment group. PDL produced the best treatment for scar texture and ILS lead to greater adverse reactions
Layton ¹²³	2	RCT	CS vs ILS vs untreated control	K	11 patients (2ethnicity or skin type) with multiple acne K scars, no exclusion criteria stated	Scar height, depth, blood flow & pliability	CS & ILS (TA 5 mg/mL);?1-3 treatments	4 months (prospective)	+CS > +ILS	Both treatments significantly improved height and pliability, with vascular keloid lesions responding better. The CS group had a significant positive difference compared to the ILS scars

(Continued)

TABLE 51-9—Monotherapy and Polytherapy Steroid Treatment Modality Published Clinical Trials (Continued)

Steroids	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Asilian ¹⁵⁰	2	RCT	ILS vs ILS & 5-FU vs ILS & 5-FU & PDL	HT & K	69 patients (ethnicity or skin type) with HT or K scars ≥10mm long, excluded patients who had received scar treatment in past 6 months, those pregnant, planning to conceive, or with renal, liver or blood count abnormalities	Scar erythema, pliability, height symptoms & size	ILS (TA 10 mg/mL); 1/week for 8 weeks, 5-FU (40 mg/mL); 1/week for 8 weeks, PDL: at 0, 4 & 8 weeks	3 months (prospective)	+ILS & 5-FU & PDL > +ILS & 5-FU > ILS	All groups demonstrated improvements in nearly all measures but these were statistically more significant in the ILS & 5-FU and ILS & 5-FU & PDL groups. Overall efficacy of ILS & 5-FU was comparable to ILS & 5-FU & PDL, but ILS & 5-FU & PDL produced better results.
Daroughheh ¹⁴⁶	2	RCT	ILS vs ILS & 5-FU	HT & K	40 patients (ethnicity or skin type) with HT or K scars, ≥10mm long, excluded if received prior scar treatment in last 6 months or failed renal, liver or blood count tests, or pregnant	Scar erythema, symptoms, pliability, height, size & overall scar appearance	ILS (TA 40 mg/mL); 1/week for 8 weeks ILS (TA 40 mg/mL) & 5-FU (50 mg/mL); 1/week for 8 weeks	3 months (prospective)	+ILS & 5-FU	Both treatment groups demonstrated an acceptable improvement in nearly all parameters measured, this was more significant in the ILS & 5-FU group, and patients felt the polytherapy outcome was more acceptable.
Darzi ¹⁴⁷	2	RCT	β-RXT vs β-RXT & exc & β-RXT vs Exc & β-RXT vs ILS	HT & K	65 patients (ethnicity or skin type) with 100 K or HT scars, no exclusion criteria stated	Scar symptoms, height & reoccurrence	β-RXT: 400cGY 2/week, ≤16Gy total β-RXT & exc & β-RXT: 400cGY 2/week, ≤16Gy, exc & repeat course Exc & β-RXT: Exc & 400cGY 2/week, ≤16Gy ILS (TA 20-40 mg/mL; 4 treatments every 1-2 weeks	<10 years (prospective)	+β-RXT (NS) -β-RXT & exc & β-RXT (NS) +Exc & β-RXT (NS) +ILS (NS)	β-RXT alone eradicated 55% of symptoms but only reduced scar height by 11%. Surgical excision and β-RXT postoperatively yielded a 67% success rate, rising to 75% if delivered with 48 hours of surgery. ILS reduced 72% of symptoms and completes flattening in 64% of lesions. There was no advantage found in receiving preoperative β-RXT.

Polytherapy								
Sclafani ¹⁶⁵	2	RCT	Exc vs Exc & ILS vs Exc & RXT (10Gy) vs Exc & RXT (7Gy)	K	42 patients (ethnicity or skin type) with 50 earlobe K scars, no exclusion criteria stated	Overall scar appearance & reoccurrence	Exc & ILS: injections day 0 & 3 further treatments Exc & RXT: 1 fraction of 10Gy or 7Gy	12 months (prospective)
Darougheh ¹⁴⁶	2	RCT	ILS vs ILS & 5-FU	HT & K	40 patients (ethnicity or skin type) with HT or K scars, ≥10mm long, excluded if received prior scar treatment in last 6 months or failed renal, liver or blood count tests, or pregnant	Scar erythema, symptoms, pliability, height, size & overall scar appearance	ILS (TA 40 mg/mL): 1/week for 8 weeks ILS (TA 40 mg/mL) & 5-FU (50 mg/mL): 1/week for 8 weeks	3 months (prospective)
Omraniard ¹⁴⁸	2	RCT	PDL vs ILS & pressure vs erbium laser	HT	120 patients (Fitzpatrick skin scale III) with HT scars ≥4cm long, <1 year old, excluded if received previous treatment within last 6 months	Scar pigmentation, vascularity, pliability & height	PDL/ILS (TA 5–10 mg/mL)/ erbium: no. of treatments, every 4 weeks pressure therapy: garments	≤12 months (prospective)
Manuskiatti ¹⁴⁵	2	RCT	PDL vs ILS vs 5-FU vs ILS & 5-FU vs untreated control	HT & K	10 patients (Fitzpatrick skin type I-IV) with HT and K sternotomy scars, ≥6 months old, excluded if previously treated	Scar height, erythema, pliability, overall scar appearance & histology	PDL/ILS (TA 20 mg/ml): 6 treatments, 4 week intervals 5-FU (50 mg/ml): 10 treatments, every 2–4 weeks ILS (TA 1 mg/mL) & 5-FU (45 mg/ml): 10 treatments, every 2–4 weeks	≤8 months (prospective)

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; PL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; ILS, intralesional steroid; IL, intrallesional steroid; Exc, excision; ILExc, intralesional excision; ELExc, extrallesional excision; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

6–12 cm², 80–120 mg) every 1–2 weeks and courses were repeated if necessary. The monotherapy groups were evaluated for reduction in scar height and symptomatic benefits, while the polytherapy groups were rated on reoccurrence only. Although no formal statistical analysis was completed, ILS fared better than β-RXT (400 cGy every 2 weeks up to 16Gy total) alone for reducing symptoms by 72% compared to 55%, and flattening 64% of lesions compared to 11%. Although a simple randomization method was employed, this did not include entering HT scars into the surgical excision groups. Therefore, this poses a difficulty when directly comparing treatment groups to evaluate the overall effect in raised scarring. Treatment regimen proves important, when Sproat¹⁰⁶ (described previously) administered only one ILS (TA 10 mg/mL) injection, this failed to prove beneficial in comparison to 12 weeks of SGS therapy. Furthermore, Layton's¹²³ (described previously) ILS (TA 5 mg/mL) injection schedule also appeared to lack a strict routine follow-up and readministration of the drug, therefore ILS treated keloid lesions did not respond as well as CS.

An attempted systematic review¹⁵⁹ rated level 3 evidence, assessed 61 articles of patients with clinically 'active' keloid scars to explore the most effective concentration and frequency application of TA injections. Overall, no studies were identified which fitted the strict inclusion criteria stated. This may be caused by the long-term nature of keloid scarring and the frequent path of failed treatments patients have endured; therefore finding subjects with keloid scars who have not receive any form of clinical or surgical treatment (as set out in the study inclusion criteria) is undoubtedly a difficult task. Other monotherapy studies (LOE-4) reported positively attributed results to ILS therapy, these included downgraded case-control studies,¹¹⁰ low-quality nonrandomized comparative studies^{122,160–162} or case-series accounts.^{163,164} Four RCTs (LOE-2)^{145,146,148,165} exist to examine the effect of ILS as a polytherapy adjuvant treatment. As described previously, when ILS is combined with 5-FU significant improvements are observed in parameters measured and this occurs faster and patients perceive this as more acceptable.^{145,146} When used in conjunction with pressure therapy in a large trial (n=120), HT scars benefited significantly post-treatment but other modalities fared better¹⁴⁸. In comparison to RXT therapy, post-surgical keloid scar excision, ILS was not as effective at preventing reoccurrences.¹⁶⁵ After surgery and ILS 33% regrew in contrast to only 12.5% after RXT and patients were more likely to complete RXT treatment.

One level 3 case-control study utilized TA (0.1%) in a topical steroid preparation in conjunction with a liquid occlusive and hydrating agent.¹⁵⁶ Forty-one patients with HT (n=32) and keloid (n=9) lesions applied the liquid compound twice a day for 2–5 months. A nonvalidated evaluation scale was employed to assess the scars in comparison to control lesions by the study author. Overall, all scar symptoms were relieved and a significant response was observed in 84% of HT scars in comparison

to 44% of keloid scars. All other polytherapy low-quality nonrandomized comparative trials^{72,149,160,162,166–171} or case-series^{84–87,121,151,152,154,157,158,172–178} reports of level 4 evidence, confirmed the positive addition of ILS, although some combinations were more favorable than others.

SURGERY

Surgery is a common management option for HT or keloid scars. This may be applied with an aesthetic or functional aim, such as HT burn scars may require release to prevent joint contractures.¹ Whereas, recurrent HT and keloid lesions require careful risk-benefit evaluation, often involving a clinically reasoned preoperative plan for adjuvant postoperative management strategies.³⁰ Keloid surgery normally focuses on two key objectives: (1) to resect or (2) to debulk. Keloid excision alone is associated with a high rate of reoccurrence (45–100%), therefore tissue resections should be combined with adjuvant therapy.⁶⁰ Combining surgery with ILS has been previously reported to reduce the reoccurrence by 50%, and if combined with perioperative RXT therapy this could be reduced to 10%.^{60,147,179,180} Debulking procedures alternatively aim to relieve patient symptoms and promote quality of life.^{44,181} This may include removing infected tissue tracts which often occur in hair-bearing regions of the scalp or anterior chest,¹⁸² or simply reducing mass so it does not show through clothing.⁴⁴ Some authors suggest adjuvant therapy post mass reduction should be addressed with caution because of the potential for excessive exposure to toxic therapies (e.g., RXT) or the side-effects of the cumulative use of other treatments (e.g., corticosteroids)²⁷.

Many different types of surgical excision strategies are available for keloid and HT scar revision. These include linear closure, excision with skin grafting, z-plasty, w-pasty and a flap coverage if other options fail.⁵⁷ Careful surgical incision along the lines of tension, not crossing them and closure without skin tension is critical.¹⁸³ Serial scar excisions may be applied for large keloids involving repeated intralesional excision procedures, to avoid a build-up of skin tension before a final extralesional excision, incorporating a margin of normal skin.^{184–186} Some authors have described a core excision procedure in which the fibrous keloid is excised to leave the epidermis and thin dermal layer to resurface the defected area.^{187,188} Tissue-engineered skin-substitute grafts composed of an artificial dermis of purified bovine collagen and human fibroblast supporting keratinocytes have also been trialed.¹⁷⁸ The type of suture material used is a controversial topic and has been found not to affect rates of HT scarring in the face.¹⁸⁹ However, others have recommended nonabsorbable sutures to be applied in regions of high tension such as the chest and shoulder girdle because of skin tension levels in that region.^{27,190}

Although surgical excision in the pathogenic scar population is rarely carried out in isolation clinically, six studies (LOE-2: 1, LOE-4: 4, LOE-5: 1) were found which evaluated

surgery alone for keloid^{165,171,181,187,191} and hypertrophic¹⁸⁶ scars (Table 51-10 and its electronic version). One RCT¹⁶⁵ included 42 patients with 50 keloid earlobe scars, however only 31 participants completed treatment and were available for follow-up at 12 months. These individuals received surgical excision only (n=3), surgical excision and ILS (n=12, treated with TA 40mg/mL intraoperatively and 3 further treatments), surgical excision and RXT postoperatively (n=16, either at the randomly assigned 10Gy or 7Gy) using either superficial x-rays or electron beams. No statistically significant difference were observed between the groups that completed treatment, although the low completion rate particularly in the excision-only group may be attributed to recurrence during this time.

Berman¹⁷¹ completed a retrospective cohort study (LOE-4) which compared the recurrence rate of keloids treated by excision alone with the results of postoperative TA or interferon (INF)- $\alpha 2\beta$. Patients lost to follow-up were assumed to have reoccurred which may have affected the study analysis of 74 cases and length of postsurgery observation varied dramatically up to 47 months, but with a mean time of 7 months. Based on these facts, recurrence rates after excision alone were thought to be 51% and this was significantly less effective than excision and INF- $\alpha 2\beta$. Another study incorporating extralesional scar excision, compared this surgical technique to and without the addition of 5-FU.¹⁹¹ Scars receiving combination therapy were perceived to improve greater than excision alone. Assessments were completed by a blinded clinician using a nonvalidated version of the VSS, but only 50% (average) patients attended each review time-point up to 6 months and no recurrence data was presented. Intralesional excisions of HT facial scars have also provided good aesthetic results,¹⁸⁶ and keloid scar flap core excision procedures have demonstrated no recurrence after the absence of adjuvant therapy¹⁸⁷ in two case-series studies (LOE-4). Other authors¹⁸¹ have advocated the use of regular debulking surgery before the inevitable recurrence in severe aggressive keloid disease. Polytherapy is a frequent strategy especially in the management of keloid scars and three RCTs (LOE-2)^{147,165,192} have examined the use of surgical excision with other treatments options. An excision procedure combined with postoperative β -RXT can yield a 67% success rate in preventing recurrence in keloid lesions with a long-term follow-up period (up to 10 years).¹⁴⁷ Over shorter monitoring periods, two out of 16 keloid scars reoccurred when treated with the same adjuvant, as opposed to four out of 12 scars after excision and ILS.¹⁶⁵ The addition of IFN- γ failed to significantly improve the effect of excision surgery to prevent regrowth of keloid lesions and after 12 weeks, 40% had recurrence.¹⁹²

Other level 4 evidence of non-randomized comparative studies,^{92,166–169,171,191,193–195} case series,^{84,85,151,154,157,158,174,177,184,196–226} and case reports,^{86,90,178,188,227,228} with adjuvant RXT, IFN, ILS, 5-FU, verapamil, imiquimod, mitomycin C, pressure therapy and various SG products, have been reported

with overall positive results to improve cosmesis and prevent recurrence. One case report¹⁷⁸ also documented the benefit of staged surgery incorporating tissue-engineered allografts to reduce the depth of the patient-derived tissue graft required to close a large lesional defect on the sole of the foot. Another report¹⁸⁸ illustrated a similar core excision procedure as described previously but via an autograft route rather than a flap methodology.

LASER

Laser therapy has evolved over the past 20 years into a potential key treatment strategy for the management of HT and keloid scars.²²⁹ The early promise shown by carbon dioxide (CO₂) lasers for the excision of keloid scars failed to curb their regrowth and recurrence, but newer CO₂ models have proved to be more effective.^{60,88,230} The outcome of lasers is tissue-specific and dependent on the wavelength applied because of the oxyhemoglobin absorption peak at 542 nm.²³¹ Lasers commonly applied in the management of raised scarring are neodymium:yttrium-aluminum-garnet (Nd:YAG, 1064 nm), CO₂ (1060 nm), intense pulsed light (IPL) (515-645 nm), erbium (1550 nm) or pulsed-dye laser (PDL). Currently the PDL wavelengths 585 nm and 595 are most frequently used therapeutically.^{58,232} PDL focuses on the principle that hypervascularity has a key role in scar appearance. The proposed mechanism centers around selective photothermolysis by which direct energy is absorbed by oxyhemoglobin, leading to thermal injury in the microvasculature and reducing collagen by thrombosis and ischemia.²³³ Levels of decreased growth factor may occur because of destruction of the vascular supply which disrupts the stimulus from endothelial cells and fibroblasts.⁸ Additionally, keloids regress following PDL-induced reduction in transforming growth factor (TGF)- β_1 expression, fibroblast proliferation and the deposition of type III collagen.^{234,235} Wound angiogenesis may also be controlled to minimize scarring by early PDL intervention.⁵⁸

The primary indication for PDL is to reduce scar redness, but it can also reduce scar volume and improve texture.^{57,58} Laser may also aid to diminish the intense pruritus experienced after a burn injury during the healing process and scar maturation.²⁷ However, multiple treatments are required to provide a better scar outcome and are made possible due to the low adverse-effect profile.²³⁶ Laser therapy is safe in dark skinned individuals although hypo- and hyperpigmentation can occur.²³⁷ The development of post-therapy itching and purpuric spots, which resolve within a week is often documented.^{150,237} Typically 1-24 treatment sessions at 4-8 week intervals have been administered.^{113,145,238–240} Ultimately, the exact treatment protocol, laser wavelengths, energy fluences and adjuvant therapies selected all influence the therapeutic response and long-term outcome in problematic scarring lesions.

(text continued on page 786)

TABLE 51-10—Monotherapy and Polytherapy Published Clinical Trials: Surgical Excision Treatment

Surgical Excision	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
Scalfani ¹⁶⁵	2	RCT	Exc vs Exc & ILS vs Exc & RXT (10Gy) vs Exc & RXT (7Gy)	K	42 patients (?ethnicity or skin type) with 50 earlobe K scars, no exclusion criteria stated	Overall scar appearance & reoccurrence	Exc & ILS: injections day 0 & 3 further treatments Exc & RXT: 1 fraction of 10Gy or 7Gy	12 months (prospective)	+Exc & RXT (10Gy or 7Gy) (NS)	No statistically significant difference was observed between the groups, RXT appears to be simpler, has a better patient compliance and is more effective than ILS in preventing K scar reoccurrence.
Darzi ¹⁴⁷	2	RCT	β-RXT vs β-RXT & exc & β-RXT vs Exc & β-RXT vs ILS	HT & K	65 patients (?ethnicity or skin type) with 100 K or HT scars, no exclusion criteria stated	Scar symptoms, height & reoccurrence	β-RXT: 400cGY 2/ week, ≤16Gy total β-RXT & exc & β-RXT: 400cGY 2/ week, ≤16Gy, exc & repeat course Exc & β-RXT: Exc & 400cGY 2/week, ≤16Gy ILS (TA 20-40 mg/mL: 4 treatments every 1-2 weeks	<10 years (prospective)	+β-RXT (NS) -β-RXT & exc & β-RXT (NS) +Exc & β-RXT (NS) +ILS (NS).	β-RXT alone eradicated 55% of symptoms but only reduced scar height by 11%. Surgical excision and β-RXT postoperatively yielded a 67% success rate, rising to 75% if delivered with 48 hours of surgery. ILS reduced 72% of symptoms and completes flattening in 64% of lesions. There was no advantage found in receiving preoperative β-RXT

Sclafani ¹⁶⁵	2	RCT	K	Exc vs Exc & ILS vs Exc & RXT (10Gy) vs Exc & RXT (7Gy)	Overall scar appearance & reoccurrence 42 patients (?ethnicity or skin type) with 50 earlobe K scars, no exclusion criteria stated	Exc & ILS; injections day 0 & 3 further treatments Exc & RXT: 1 fraction of 10Gy or 7Gy	+Exc & RXT (10Gy or 7Gy) (NS)	No statistically significant difference was observed between the groups, RXT appears to be simpler, has a better patient compliance and is more effective than ILS in preventing K scar reoccurrence.
Broker ¹⁹²	2	RCT	K	Exc & IFN-γ vs Exc & placebo control	9 patients (?ethnicity or skin type) with ≥2 K lesions, extensive exclusion criteria	Exc, IFN-γ: 10 treatments, 1/ week	- IFN-γ (NS)	There was no significant difference in scar size or height between the IFN-γ and the placebo control group at 3 months. Small sample size prevented further time point analysis. IFN-γ did not prevent reoccurrence of K scarring in this study.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; ILS, intralesional corticosteroid; IL, intrallesional; Exc, excision; ILExc, intralesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

Six RCTs (LOE-2, see Table 51-11 and its electronic version)^{113,145,148,236-238} have compared the efficacy of PDL on HT and keloid lesions. PDL was evaluated against IPL in 15 patients receiving both treatment modalities via 2 applications, 2 months apart to alternative HT scar regions.²³⁸ Randomly presented post-operative side-by-side photographs were scored using a nonvalidated scale for improvement by a single physician. The PDL treated scars benefitted 80% after two treatments in comparison to 65% change in the IPL scars. There was no significant difference, however between study treatments arms and patients rated IPL as a more painful therapy. Laser pain also caused six patients to drop out of Wittenberg's¹¹³ study, where PDL was no more effective than SGS.

When PDL and erbium laser were compared to combined ILS and pressure therapy, both laser modalities proved significantly better at treating HT scars¹⁴⁸. The large single blinded and randomized trial employed three trained clinicians to minimize inter-observer error when assessing using the VSS and dial caliper. Overall, the PDL proved more effective than the erbium laser when patient opinions were evaluated (70% scar improvements compared to 65%), but the actual total number of monthly treatments received (up to a maximum of 12) was not provided. In pulse width studies²³⁷ of the same sternotomy scar comprising 19 patients treated on 3 occasions with a 595nm laser at either 0.45- or 40ms at monthly intervals, PDL significantly decreased scar volume. The previously untreated scars were randomized and blindly assessed using a range of validated tools over 6 months. Segments treated with PDL (pulse width 0.45 ms) reduced in size and had improved pliability to a statistically significant degree, but neither pulse width significantly affected erythema. Spots of purpura were noted in 21% of the PDL 0.45 ms group only. An earlier study by the same group,²³⁶ divided 10 similar scars into 4 segments and randomly treated each with 585 nm PDL at an energy density fluence of 3, 5 and 7 J/cm² every 4 weeks for 6 total treatments. Clinical assessment of scar height and erythema was carried out as before, and pliability was recorded using a standard scale. A significant improvement in all parameters was noted in all laser treated regions but no statistical difference was determined between fluences, although a trend for better response with lower fluences is observed. Other authors concluded that PDL significantly improved HT and keloid scar appearance and produced the best results for scar texture, but was no more beneficial than ILS, 5-FU or ILS & 5-FU.¹⁴⁵

Five case-control studies (LOE-3) compared PDL with untreated controls and statistically significant improvements were documented in all scar color, height, texture and symptoms recorded.²⁴¹⁻²⁴⁵ However, in one study these were not significant when compared to the normal maturation process in the control HT scar.²⁴⁴ Liew²⁴³ determined that PDL treatment should be considered in the early management of HT scarring, but treatment may need to continue past the 3 month point as initial scar

improvements decreased at 3 and 6 months post therapy completion.²⁴³ The positive results achieved by one PDL case-control study²⁴² after 2 months were in contrast to other research, which suggested that objective improvements could be observed from 16 weeks onwards.²³⁶ Bowes²⁴⁵ study additionally compared the 532 nm Nd:YAG laser using two different modes of pulsing energy delivered (Q-switched or variable pulse). The Nd:YAG (Q-switched) results were comparable to the PDL, but patients preferred the results achieved by the Nd:YAG in pigmented HT scars. Further nonrandomized comparative trials and case-series (LOE-4) provided positive evidence to support the use of PDL,^{117,246-248} CO₂ laser,⁸⁸ IPL,^{239,249} Nd:YAG¹⁷⁵ and erbium laser.²⁵⁰ Two additional case-series studies negated any benefits from CO₂ laser²⁴⁰ or PDL²⁵¹ and two case reports (LOE-5)^{230,252} supported the application of CO₂ and KTP for raised scarring. One polytherapy RCT¹⁵⁰ previously described documented additional beneficial results when PDL was added to the ILS and 5-FU treatment programme. Here PDL provided the added advantage that it lightening pigmented lesions to increase patient satisfaction, but this treatment modality did induce 7-10 days of pruritic symptoms. Other nonrandomized comparative studies (LOE-4),^{88,149} cases-series (LOE-4)^{89,173,176} and case reports (LOE-5)⁹⁰ were all favorable to the addition of laser in polytherapy management.

RADIOTHERAPY

Irradiation (RXT) treatment is considered an option in particular for recurrent keloid lesions.⁵⁹ RXT can be administered via the techniques of brachytherapy, β-RXT, superficial x-ray or low-energy electron beam transmission. It is hypothesized that an improved balance between collagen synthesis and degradation is achieved by the irradiation destruction, which takes place in the fibroblasts, connective tissue stem cells, extracellular matrix gene expression and other acute inflammatory cells^{153,177}. Irradiation monotherapy however has limited success in reducing scar height and symptoms.¹⁴⁷ Therefore, the use of RXT with other treatment modalities, especially surgery has been suggested to improve effectiveness and can provide preventative success rates between 67-98%.^{147,193,200,227} This is often initiated immediately postoperatively or within 48 hours,^{147,194,202,203} with the total dose limited to 7.5-40 Gy.^{203,205,208,253} Multiple descriptions of various treatment intervals (1-11 fractions), single dose levels (1.5-7 Gy) and cumulative doses exist.^{177,195,201,203,208,227}

Most safety concerns associated with this scar treatment modality are in respect to the risk of inducing malignant tumors for the management of essentially a benign condition. Nevertheless when surveyed, 78% of radiation oncologists recognize that RXT is an acceptable treatment for keloid scarring.^{254,255} Therefore, it is essential appropriate dose therapy is provided in conjunction with the adequate provision of surrounding healthy

(text continued on page 790)

TABLE 51-11—Monotherapy and Polytherapy Published Clinical Trials: Laser Treatment Modality

Laser	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
Bellew ²³⁸	2	RCT	PDL vs IPL	HT	15 HT scars (Fitzpatrick skin type I-III) 6-8 weeks old, excluded if received previous scar treatment	Overall scar appearance, pain	PDL/IPL: 2 treatments, 2 months apart	4 months (prospective)	+PDL +IPL	PDL and IPL are effective and significant treatment outcomes for HT surgical scars from baseline comparisons, but neither modality performed to a statistically significant level above another. Patients rated IPL more painful than PDL.
Wittenberg ¹¹³	2	RCT	SGS vs PDL vs untreated control	HT	20 patients (Fitzpatrick skin type I-V) with a linear HT scars ≥ 8cm long, excluded if received scar treatment in previous 2 months,	Scar blood flow, pliability, volume, symptoms & histological biopsy assessment	SGS: ≥ 12 hrs/day, PDL: 4 treatments at 8 week intervals	10 months (prospective)	-SGS (NS) -PDL (NS)	Overall significant reduction in blood flow, volume and pruritus was recorded during the monitored phase in all scar regions. There was no difference in the improvement in scars sections treated with SGS or PDL compared to control sections.
Manuskiatti ²³⁶	2	RCT	PDL vs PDL vs PDL (at different fluences) vs untreated control	HT	10 patients (Fitzpatrick skin type I-IV) with HT stenotomy scars, ≥6 months old, excluded if received prior treatment	Scar height, erythema, pliability & overall appearance	PDL: 6 treatments, every 4 weeks	8 months (prospective)	+PDL	Scar parameters improved significantly in all PDL treated scar areas, but there was no significant difference in the outcome dependent on the laser fluence administered (although there was an improvement trend towards lower fluences). Multiple treatment sessions achieved greater response.
Omraniard ¹⁴⁸	2	RCT	PDL vs ILS & pressure vs erbium laser	HT	120 patients (Fitzpatrick skin scale III) with HT scars ≥ 4cm long, <1 year old, excluded if received previous treatment within last 6 months	Scar pigmentation, vascularity, pliability & height	PDL/ILS (TA 5-10 mg/mL)/ erbium?: no. of treatments, every 4 weeks pressure therapy: garments	≤ 12 months (prospective)	+ILS & pressure < +PDL +erbium laser	All three groups significantly improved post treatment, but the results in the PDL and erbium laser treatment groups was significantly higher than the ILS & pressure group.

(Continued)

TABLE 51-11— Monotherapy and Polytherapy Published Clinical Trials: Laser Treatment Modality (Continued)

Laser	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Manuskiatti ¹⁴⁵	2	RCT	PDL vs ILS vs 5-FU vs ILS & 5-FU vs untreated control	HT & K	10 patients (Fitzpatrick skin type I-IV) with HT and K sternotomy scars, ≥6 months old, excluded if previously treated	Scar height, erythema, pliability, overall scar appearance & histology	PDL/ILS (TA 20 mg/mL): 6 treatments, 4 week intervals 5-FU (50 mg/mL); 10 treatments, every 2-4 weeks ILS(TA 1 mg/mL) & 5-FU (45 mg/mL); 10 treatments, every 2-4 weeks	≤8 months (prospective)	+PDL +ILS +5-FU +ILS & 5-FU	Clinically and statistically all scars improved after ILS, ILS & 5-FU, 5-FU and PDL comparably. ILS, ILS & 5-FU and 5-FU alone resulted in faster resolution and better scar induration than the PDL treatment group. PDL produced the best treatment for scar texture and ILS lead to greater adverse reactions
Manuskiatti ²³⁷	2	RCT	PDL vs PDL (different pulse widths)	HT & K	19 patients (Fitzpatrick skin type III-IV) with HT and K sternotomy scars, ≥6 months old, excluded if previously treated	Scar volume, height, erythema & pliability	PDL: 3 treatments, 4 week intervals	6 months (prospective)	+PDL (pulse width 0.45 ms)	PDL of both pulse widths significantly decreased the volume of scar segments. PDL (pulse width 0.45 ms) was statistically more effective in reducing scar size and improving pliability than PDL (pulse width 40 ms). Pulse width did not significantly effect scar erythema.

Polytherapy	Asilian ¹⁵⁰	2	RCT	ILS vs ILS & 5-FU vs ILS & 5-FU & PDL	HT & K 69 patients (?ethnicity or skin type) with HT or K scars ≥ 10mm long, excluded patients who had received scar treatment in past 6 months, those pregnant, planning to conceive, or with renal, liver or blood count abnormalities	Scar erythema, pliability, height symptoms & size ILS (TA 10 mg/ mL); 1/week for 8 weeks, 5-FU (40 mg/ mL); 1/week for 8 weeks, PDL: at 0, 4 & 8 weeks	+ILS & 5-FU & PDL > +ILS & 5-FU > ILS 3 months (prospective)	+ILS & 5-FU & PDL > +ILS & 5-FU > ILS All groups demonstrated improvements in nearly all measures but these were statistically more significant in the ILS & 5-FU and ILS & 5-FU & PDL groups. Overall efficacy of ILS & 5-FU was comparable to ILS & 5-FU & PDL, but ILS & 5-FU & PDL produced better results.
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RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; ILS, intralesional steroid; IL, intralesional; Exc, excision; ILExc, intralesional excision; ELExc, extrallesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

tissue protection, in particular the thyroid and mammary glands.²⁷ Only one RXT RCT (LOE-2, see Table 51-12 and its electronic version)¹⁴⁷ was evaluated which included RXT treatment alone, although β -RXT (twice weekly 4Gy, up to \leq 16Gy) monotherapy only eradicated 55% of symptoms and scar height by 11%. This improved considerably when surgical excision preceded the β -RXT and yielded a 67% success rate in preventing recurrences, rising to 75% if delivered with 48 hours of surgery. There was no advantage found in receiving preoperative β -RXT. Other authors (LOE-4)^{193,195} also found surgery and RXT more effective for keloid and HT scar management than RXT alone, especially if treatment was initiated up to 72 hours after excision with a single dose of 9Gy or greater.¹⁹⁵ Brachytherapy was preferred by Guix¹⁹³ for improved treatment selectivity and a lower degree of normal tissue irradiation than superficial x-rays or electron beam. In two non-randomized comparative dose evaluation studies (LOE-4),^{256,257} one assessed the benefits of receiving a 20Gy dose in 4 fractions either once a week, or twice a week.²⁵⁶ A positive response was defined as flattening of the lesion, relief of symptoms and restraint from further growth. When RXT was administered twice weekly, a successful response was recorded in 92% of lesions in comparison to 81% in those receiving weekly RXT. Alternately, Ogawa²⁵⁷ recommended that a traditional standardized protocol should be abandoned for a site-specific or scar characteristic protocol such as 10Gy in 2 fractions over 2 days for earlobe scars and 20Gy in four fractions over 4 days for keloid and intractable HT scars. A monotherapy case-series (LOE-4) study of 64 patients also reported 86 unresectable keloid scars has 97% significant regression 18 months post 37.5Gy RXT (received in 5 weekly fractions). Meanwhile the variable sites, individual and scar-specific propensity for recurrent disease limit the extent to which direct comparisons can be drawn when receiving such widespread therapy as irradiation. Twenty-seven additional polytherapy studies incorporating pre-RXT surgical excision provided positive level 2 (described previously),¹⁶⁵ level 4^{168,177,184,194,197,198,200-216,253} and level 5^{227,228} evidence, except one study of 'resistant keloids'.¹⁹⁹

5-FLUOROURACIL

5-Fluorouracil (5-FU) is a nucleotide (pyrimidine) analog with antimetabolite activity, which is a logical therapeutic modality for pathogenic scarring which has been shown to exist in a hypermetabolic state.²⁵⁸ The 5-FU is enzymatically converted intracellularly into its active substrate which is ultimately incorporated into DNA in place of uracil, where it inhibits DNA synthesis.⁸⁷ Cells proliferating rapidly, such as fibroblasts which are synthesizing increased amounts of DNA are preferentially targeted by 5-FU.¹⁵² *In-vitro*, both fibroblast proliferation and fibroblast-populated collagen lattices have demonstrated

a dose-related decline when treated with fluorouracil¹⁵², therefore it is believed to reduce postoperative scarring by suppressing fibroblast proliferation.^{149,259} Histopathological improvements have shown diminished hyalinization of collagen fibres, reduced vascularity prominence and flattening of dermal papillae *in-vivo*²⁶⁰. These characteristics of the drug as a chemotherapeutic agent have successfully broadened its use.

5-FU is frequently administered via intralesional injection (single or multiple doses), or at the time of surgery, the wound is exposed to 5-FU-soaked sponge pads for around 5 minutes before saline irrigation.^{191,260,261} The safety and efficacy of the 5-FU compound in surgery has been documented in long-term follow-ups with a multicenter study.²⁶² Side-effects are similar to other intralesionally administered drugs such as pain at the injection site, and short purpura formation and ulceration.^{149,261,263} Pigmentary disturbance (hyperpigmentation) can also occur, however this was reported not to be permanent and improved after discontinuation of treatment.^{87,263} When used post surgical excision, no wound dehiscence has been reported even when sutures were removed at 7 days.¹⁹¹

Clinically a number of studies exist utilizing 5-FU (see Table 51-13 and its electronic version). In Darzi's RCT (LOE-2, described previously),¹⁴⁷ scars statistically improved after receiving intralesional therapy with all treatment study arms, but no significant difference was determined for scar sections treated with 5-FU alone or in combination. Alternatively, a small non-randomized comparative study (LOE-4)¹⁴⁹ of 5 patients comparing various treatment regimes of 5-FU alone, 5-FU and ILS and 5-FU, ILS and PDL determined that the therapy was safe and effective for HT scars, not just keloids. In particular, scars that were most inflamed, red in colouration, firm and symptomatic responded more significantly to 5-FU mono- or polytherapy. Three case-series studies^{260,261,263} documented that the majority of scars improved by over 50%,²⁶¹ with half of patients observing 50% scar flattening²⁶³ and 95% of keloid scars reducing in volume after 5-FU therapy alone.²⁶⁰ Overall, no patients failed treatment and 5-FU was as effective as other keloid monotherapies.²⁶¹ The effects and recurrence rates correlated with the duration of the lesion and not the scar size^{260,263} Further polytherapy studies have acknowledged the positive therapeutic benefits of 5-FU with ILS (LOE-2: 2, LOE-4: 2),^{146,150,152,170} excision and 5-FU (LOE-4: 2)^{191,196} and 5-FU with multiple therapy components (LOE-2: 1, LOE-4: 1, LOE-5: 1).^{87,150,170}

INTERFERON

This promising method of scar management has originated from recent attempts to manipulate wound healing with various recombinant growth factors and interferons (IFN)¹⁹². This therapy focuses on interrupting the cell proliferation and activation of apoptotic pathways in raised scarring. Recent studies have demonstrated an inhibitory

(text continued on page 794)

TABLE 51-12—Monotherapy and Polytherapy Published Clinical Trials: Radiation Treatment Modality

Radiation	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
Darzi ¹⁴⁷	2	RCT	β-RXT v β-RXT & exc & β-RXT v Exc & β-RXT v ILS	HT & K	65 patients (?ethnicity or skin type) with 100 K or HT scars, no exclusion criteria stated	Scar symptoms, height & reoccurrence	β-RXT: 400cGY 2/week, ≤16Gy total β-RXT & exc & β-RXT: 400cGY 2/week, ≤16Gy, exc & repeat course Exc & β-RXT: Exc & 400cGY 2/week, ≤16Gy ILS (TA 20-40 mg/mL; 4 treatments every 1-2 weeks	<10 years (prospective)	+β-RXT (NS) -β-RXT & exc & β-RXT (NS) +Exc & β-RXT (NS) +ILS (NS)	β-RXT alone eradicated 55 % of symptoms but only reduced scar height by 11%. Surgical excision and β-RXT postoperatively yielded a 67% success rate, rising to 75% if delivered with 48 hours of surgery. ILS reduced 72% of symptoms and completes flattening in 64% of lesions. There was no advantage found in receiving preoperative β-RXT.
Van de Kar ¹⁹⁹	4	Case-series	ELExc & RXT	K	21 patients (?ethnicity or skin type) with resistant 32 K scars not located on glandular tissue, excluded if pregnant or no K histology	Overall scar reoccurrence	ELExc, RXT: 12Gy, 3-4 fractions, within 24 hours & consecutive days	≥12 months (prospective)	-ELExc & RXT (NS)	The high reoccurrence rate (72% at 19 months) suggests RXT is less effective than other studies suggest, therefore surgical exc and RXT should be reserved as a last resort in the treatment of persistent K scarring.
Norris ²⁰⁰	4	Case-series	Exc & RXT	K	24 patients (?ethnicity or skin type) with K scarring, no exclusion criteria stated	Overall scar reoccurrence	Exc, RXT: 8-12Gy, 1-3 fractions, 82% within 24 hours of Exc	≥24 months (retrospective)	+Exc & RXT (NS)	Superficial X-ray therapy is effective at reducing the rate of post-excisional scar reoccurrence

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SGC, silicone gel cushion; HT, hypertrophic K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; ILS, intralesional steroid; IL, intralesional excision; ELExc, extralesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

TABLE 51-13—Monotherapy and Polytherapy Published Clinical Trials: 5-Fluorouracil Treatment Modality

5-Fluorouracil	LOE	Study Design	Evaluated Treatment Type	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Monotherapy</i>										
Manuskiatti ¹⁴⁵	2	RCT	PDL vs ILS vs 5-FU vs ILS & 5-FU vs untreated control	HT & K	10 patients (Fitzpatrick skin type I-IV) with HT and K sternotomy scars, ≥6 months old, excluded if previously treated	Scar height, erythema, pliability, overall scar appearance & histology	PDL/ILS (TA 20 mg/mL); 6 treatments, 4 week intervals 5-FU (50 mg/mL); 10 treatments, every 2-4 weeks ILS(TA 1 mg/mL) & 5-FU (45 mg/ml); 10 treatments, every 2-4 weeks	≤8 months (prospective)	+PDL +ILS +5-FU +ILS & 5-FU	Clinically and statistically all scars improved after ILS, ILS & 5-FU, 5-FU and PDL comparably. ILS, ILS & 5-FU and 5-FU alone resulted in faster resolution and better scar induration than the PDL treatment group. PDL produced the best treatment for scar texture and ILS lead to greater adverse reactions
Daroughreh ¹⁴⁶	2	RCT	ILS vs ILS & 5-FU	HT & K	40 patients (?ethnicity or skin type) with HT or K scars, ≥10mm long, excluded if received prior scar treatment in last 6 months or failed renal, liver or blood count tests, or pregnant	Scar erythema, symptoms, pliability, height, size & overall scar appearance	ILS (TA 40 mg/mL); 1/week for 8 weeks ILS (TA 40 mg/mL) & 5-FU (50 mg/mL); 1/week for 8 weeks	3 months (prospective)	+ILS & 5-FU	Both treatment groups demonstrated an acceptable improvement in nearly all parameters measured; this was more significant in the ILS & 5-FU group, and patients felt the polytherapy outcome was more acceptable.

Asilian ¹⁵⁰	2	RCT	ILS vs ILS & 5-FU vs ILS & 5-FU & PDL	HT & K 69 patients (?ethnicity or skin type) with HT or K scars ≥ 10 mm long, excluded patients who had received scar treatment in past 6 months, those pregnant, planning to conceive, or with renal, liver or blood count abnormalities	ILS (TA 10 mg/mL): 1/week for 8 weeks, 5-FU (40 mg/mL): 1/week for 8 weeks, PDL: at 0, 4 & 8 weeks	3 months (prospective)	+ILS & 5-FU & PDL > +ILS & 5-FU > ILS	All groups demonstrated improvements in nearly all measures but these were statistically more significant in the ILS & 5-FU and ILS & 5-FU & PDL groups. Overall efficacy of ILS & 5-FU was comparable to ILS & 5-FU & PDL, but ILS & 5-FU & PDL produced better results.
Manuskiatti ¹⁴⁵	2	RCT	PDL vs ILS vs 5-FU vs ILS & 5-FU vs untreated control	HT & K 10 patients (Fitzpatrick skin type I-IV) with HT and K sternotomy scars, ≥ 6 months old, excluded if previously treated	Scar height, erythema, pliability, overall scar appearance & histology PDL/ ILS (TA 20 mg/mL): 6 treatments, 4 week intervals 5-FU (50 mg/mL): 10 treatments, every 2-4 weeks ILS(TA 1 mg/mL) & 5-FU (45 mg/ mL): 10 treatments, every 2-4 weeks	≤ 8 months (prospective)	+PDL +ILS +5-FU +ILS & 5-FU	Clinically and statistically all scars improved after ILS, ILS & 5-FU, 5-FU and PDL comparably. ILS, ILS & 5-FU and 5-FU alone resulted in faster resolution and better scar induration than the PDL treatment group. PDL produced the best treatment for scar texture and ILS lead to greater adverse reactions

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGC, silicone gel sheet; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCs, intralesional cryosurgery; ILS, intralesional steroid; IL, intrallesional excision; ELExc, extralesional excision; EExc, extralesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

effect of IFNs, in particular IFN- α and IFN- γ on dermal fibroblast synthesis, collagen production and angiogenesis by reducing angiogenic factor concentrations.^{160,264} In may fibrotic disorders, local and systemic TGF- β have been implicated in the pathogenesis as fibrogenic cytokines. Keloid lesions are also known to have markedly depressed production levels of IFN- α , IFN- γ and TNF- β .²⁶⁵ It has been thought that IFN- $\alpha2\beta$ may benefit scar pathogenic features by antagonizing the effects of TGF- β and histamine.²⁶⁶ Short-term treatment of keloids with IFN- $\alpha2\beta$ has resulted in a selective and persistent keloidal fibroblast collagen normalization, glycosaminoglycans, and collagenase production and a clinical reduction in progressively enlarging keloids.^{267,268}

IFN compounds are normally administered intralesionally and by the nature of IFN treatment, a normal renal, hepatic and autoimmune function is required.^{160,192,268} Mild side effects attributed to the IFN are generalized flu-like symptoms, which occur in 74% of patients several hours after their first treatment but subside with subsequent treatments and no significant abnormalities in laboratory monitoring (serum, urinalysis or sediment) tests were observed during treatment.^{160,269,270} Intralesional injections are painful and 36% may require local anaesthetic²⁷⁰. Six monotherapy studies (LOE-2:1, LOE-4: 4, LOE-5:1, see Table 51-14 and its electronic version) were examined which included the cytokines TNF- α ,¹⁴⁴ IFN- $\alpha2\beta$,^{266,268} IFN- γ ^{270,271} and IFN- $\alpha2\alpha$ ²⁷² in therapeutic management of raised scars. The only RCT¹⁴⁴ (described previously) compared TNF- α to ILS. Both TNF- α and ILS improved scar appearance parameters after 8 weeks from baseline levels, but not to a significant level and TNF- α failed to perform as well as ILS. TNF- α did however, significantly reduce pruritus statistically after only two treatments administered in this programme. One case-controlled study²⁶⁸ evaluated the use of IFN- $\alpha2\beta$ injected intralesionally twice a week for 3 weeks compared to a placebo control. Follow-up was limited to 29 days and INF- $\alpha2\beta$ was found to be insignificant at reducing the height of mature keloid lesions. Alternatively, IFN- $\alpha2\beta$ significantly improved HT scar quality and volume after a high frequency treatment programme encompassing 76 injections over 6 months.²⁶⁶ Two small case-series^{270,271} additionally proved in favor of IFN- γ therapy. In one study, the majority of scars had complete symptomatic relief and objective changes after a month of therapy.²⁷⁰ Whereas in another,²⁷¹ after a 10-week treatment course all scars reduced in height and up to 50% in size, but the lack of follow-up after therapy completion may question the success. This is because Pittet²⁷⁰ found that 4 out of 7 patients had an increase in lesional area after completing IFN-g treatment.

When a small (n=9) RCT¹⁹² was completed to evaluate the use of INF-g post surgical excision, IFN therapy was found to be less effective than placebo treatment. Additionally, Davison¹⁶⁹ also found IFN- $\alpha2\beta$ to be less effective than post excisional ILS and the trial was stopped

prematurely because of the significantly high recurrence rates. This was in contrast to another comparative study¹⁷¹ which found IFN- $\alpha2\beta$ to be significantly better at preventing post surgical recurrence than ILS (19% in comparison to 58% recurrence), but treatment protocols were highly variable. Alternatively, if combined intralesional injections of IFN- $\alpha2\beta$ and ILS are administered statistically significant reductions in keloid height and volume are reported.¹⁶⁰

VERAPAMIL

Verapamil is a widely used calcium channel agonist, which can be used as an alternate intralesional therapy for HT and keloid scars. Calcium antagonists decrease the production of collagen in the extracellular matrix, stimulate the synthesis of collagenase and increase TGF- β activity.²⁷³⁻²⁷⁵ Depolymerization of actin filaments, altered cell shape and reduction of fibrous tissue production have also been shown to occur.^{161,276} Verapamil is a safe drug administered intralesionally and has been used topically in other fibrotic conditions to obtain successful results.^{222,277} It can be applied as a mono- or polytherapy to stabilize and prevent keloid scarring in susceptible individuals.^{92,161,221,222}

Only one parallel group comparative study (LOE-4, see Table 51-15)¹⁶¹ has evaluated the use of intralesional verapamil (1 mL of 2.5 mg/mL) against ILS in 54 patients with HT and keloid lesions. Scar improvements were assessed using the VSS and basic dimension measurements, but no blinding was described. A reduction in scar vascularity, pliability height and size was seen in both groups after 3 weeks, but changes were faster with ILS than verapamil. Outcomes were maintained up to 1 year, therefore verapamil may be a suitable alternative with less adverse side-effects to ILS in raised scarring. Three further studies (LOE-4)^{92,221,222} administered verapamil after surgical excision with positive results. Two years after treatment only 4 patients developed recurrences (n=2 keloid and n=2 HT) out of 22 receiving therapy.²²² When pressure therapy was also applied 55% of earlobe keloid scars were 'cured' after 6-28 months follow-up, with a positive trend to increased recurrence in previously treated scars.²²¹ If surgery was combined with verapamil (0.5-2 mL of 2.5 mg/mL) and SGS then various site and age matched keloids were 54% 'cured' after 18 months and recurrences were smaller in size and had a better consistency.⁹²

IMIQUIMOD

Imiquimod is a novel immune modulator that can be used to treat a variety of dermatologic conditions including basal cell carcinoma. The toll-like receptor agonist has a localized therapeutic response and is known to affect immune responses, which are both innate and cell-mediated, although the exact mechanism of imiquimod 5% cream is not fully understood.^{217,278} It has also been

TABLE 51-14 — Monotherapy and Polytherapy Published Clinical Trials: Interferon Treatment Modality

Interferon	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Monotherapy</i>										
Berman ¹⁴⁴	2	RCT	ILS vs TNF- α	K	20 patients (7ethnicity or skin type) with K scars ≥ 1 year old, ≤ 2 cm in length, extensive exclusion criteria including prior scar treatment in last 6 weeks	Scar erythema, symptoms, pigmentation, induration, volume & overall appearance	ILS (TA 20 mg/mL) or TNF- α : 2 treatments at 0 and 4 weeks	2 months (prospective)	+ILS (NS) +TNF- α	Both treatments improved several scar parameters at week 8, with ILS performing better than TNF- α although not significantly different compared to baseline. No statistical difference was apparent between groups, however TNF- α significantly reduced pruritus.
Broker ¹⁹²	2	RCT	Exc & IFN- γ vs Exc & placebo control	K	9 patients (7ethnicity or skin type) with ≥ 2 K lesions, extensive exclusion criteria	Scar size, height & overall scar appearance	Exc, IFN- γ : 10 treatments, 1/week	12-14 months (prospective)	-IFN- γ (NS)	There was no significant difference in scar size or height between the IFN- γ and the placebo control group at 3 months. Small sample size prevented further time point analysis. IFN- γ did not prevent reoccurrence of K scarring in this study.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel cushion; SGS, silicone gel sheet; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCs, intralesional steroid; IL, intralesional steroid; Exc, excision; ILExc, intralesional excision; ELExc, extrallesional excision; IPL, intense pulsed light; BM, betamethasone sodium phosphate; TA, triamcinolone acetonide; MP, methylprednisolone acetate; IFN, interferon; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

TABLE 51-15 — Monotherapy and Polytherapy Published Clinical Trials: Verapamil Treatment Modality

Verapamil	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Monotherapy</i>										
Shianthi ¹⁶¹	4	Comparative	ILS vs IL verapamil	HT & K	54 patients (ethnicity or skin type) with HT and K scars 2-10cm long, <5 years old, extensive exclusion criteria including a family history of K scarring	Scar pigmentation, vascularity, pliability, height & size	ILS (40 mg/mL) or IL verapamil (2.5 mg/mL); every 3 weeks up to ≤6 months	≤18 months (prospective)	+ILS (NS) > +IL verapamil (NS)	There was a reduction in scar vascularity, pliability, height and size seen in both treatment groups after 3 weeks, but changes were faster with ILS than IL verapamil. The outcomes were maintained at one year follow-ups after stopping treatment. IL verapamil has less adverse drug reactions and may be a suitable alternative to ILS in raised scarring.
D'Andrea ⁹²	4	Comparative	ELExc & SGS & IL verapamil vs Exc & SGS	K	44 patients (ethnicity or skin type) with various site K scars, no exclusion criteria stated	Scar size, thickness, texture & symptoms	ELExc, SGS; applied day 7-14 for 6-9 months, IL verapamil: day 0, 7, 14, 28 and during month 2	18 months (prospective)	+ELExc & SGS & IL verapamil (NS) > Exc & SGS	After 18 month reviews, K scars were cured in 54% of cases in the IL verapamil group compared to 18% in the second treatment group. Of the 36% of patients in the first group who saw reoccurrences, these were smaller in size and consistency. The authors conclude that verapamil hydrochloride is an effective preventative tool for K scars.
Lawrence ²²¹	4	Case-series	Exc & IL verapamil & pressure therapy	K	35 African American patients with 45 earlobe K scars, no exclusion criteria stated	Scar overall appearance/reoccurrence	Exc, IL verapamil: day 7-14 post-operatively & 1 month after Pressure earrings: continuously for ≥6 months	6-28 months (prospective)	+Exc & IL verapamil & pressure therapy (NS)	55% of K scars were cured by this treatment. There was a trend towards increased reoccurrence rates for previously treated K scars.
Copcu ²²²	4	Case-series	Exc & IL verapamil	K & HT	22 patients (ethnicity or skin type) with various K lesions ≤10mm wide and one HT scar, no exclusion criteria stated	Scar overall appearance, symptoms, patient satisfaction & histology	Exc with W-plasty or skin graft, IL verapamil: day 0, 7, 14, 28 and during month 2	≥ 2 years (prospective)	+Exc & IL verapamil (NS)	Two years after the treatment, 2 patients have keloid reoccurrences and 2 patients had HT scars. The authors suggest that surgical excision with W-plasty or skin grafting and IL verapamil may be a good alternative for the treatment of keloids.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGS, silicone gel sheet; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IP, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; IL, intralesional steroid; IL, intrallesional Exc, excision; ELExc, intralesional excision; ILver, IL verapamil; BM, betamethasone sodium phosphate; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

documented that imiquimod may be capable of enhancing local production of cytokines, interferons, TNF and interleukins, imparting an antifibrotic action to decrease collagen and glycosaminoglycan production.^{224,225} Imiquimod 5% cream can be applied as a polytherapy to prevent recurrences of keloids and HT scars postsurgical excision.¹⁰³ However local skin reactions do occur in 37% of cases, including erosion and erythema at the application site, this may require 1 week therapeutic break-period or occasionally some patients may be required to start every-other-day dosing.^{167,224,225} No monotherapy studies were located, but one non-randomized comparative study (LOE-4, see Table 51-16)¹⁶⁷ found topical imiquimod more beneficial than ILS after a shave excision procedure on earlobe keloids (2 of which were bilateral). Patients applied the cream daily for 8 hours for 8 weeks and after 6 months 75% of the imiquimod group were recurrence free, compared to 50% of the ILS scars. Patients in two additional positive case-series studies (LOE-4)^{217,225} applied imiquimod daily for 6-8 weeks and no evidence of recurrence was noted in any lesion after 6-12 months follow-up. The scars were asymptomatic and an excellent cosmetic results was achieved,²¹⁷ except hyperpigmentation in 64% of lesions.²²⁵ However, further studies (LOE-4:1, LOE-5:1)^{224,279} with similar regimes failed to demonstrate the efficacy of this particular combined therapy.

MITOMYCIN C

Mitomycin C is a chemotherapeutic and antineoplastic agent, which works by inhibiting DNA synthesis and fibroblast proliferation. It has previous been used for the successful management of laryngeal or tracheal stenosis¹⁰³. Mitomycin C alkylates and cross-links with DNA to inhibit DNA and protein synthesis. In in-vitro, fibroblasts treated with mitomycin C have a reduced DNA synthesis and density compared with controls.^{220,280} The inhibition of fibroblast proliferation by the therapy can decrease wound fibrosis when topically applied²⁸¹. In general, mitomycin C is well-tolerated even on new excision sites, but hyperpigmentation side-effects can be observed in rare cases.¹⁰³ One level 4 evidence comparative study (see Table 51-17)¹⁶⁶ evaluated the effectiveness of applying mitomycin C to one keloid out of two resected scar wound beds (n=15 patients) for 5 minutes at a concentration of 0.4 mg/mL prior to formal closure. All patients applied vitamin A and E cream to both wounds and one month after surgical excision both scars received ILS. The general scar appearance was monitored for signs of recurrence with no blinding and two patients were followed up by telephone rather than visually assessed. Overall, no statistically significant difference was observed between treatment groups. In three other small (n=28 in total) cases-series studies (LOE-4),^{219,220,226} mitomycin C proved a favorable polytherapy after surgical excision. A successful outcome and prevention rate of 80²²⁶- 90%²²⁰ was documented in keloid scars after a

14 month maximum follow-up. However, the terms by which a treatment is defined as successful or effective need to be better defined for comparative purposes in this complex patient group. For example, in Talmi's²¹⁹ study all patients were satisfied with the results after long-term follow-up (≤ 14 months) rated on a nonvalidated measure but complete keloid disappearance was only evident in 2 patients at 2 months.

Pressure

Pressure therapy has been a standard treatment for post-burn HT scars and is used as a frequent polytherapy for earlobe keloids. A wide range of pressure therapy devices exist, from fabric pressure garments often custom-designed for specific regions of the body, to the vast array of clips available for site-specific regions like the ear.^{85,174,282} The posterior auricular region is one of the most common and most difficult locations for pressure therapy that a keloid scar can develop. In this instance, a custom-made silicon ear mould can apply pressure homogeneously to the cartilaginous and lobular region. Wearing pressure garments can be uncomfortable, painful, hot and embarrassing, and as a consequence is challenging for the patient and subsequently low compliance is common.²⁸³

The application of constant scar pressure can potentially occlude capillaries and restrict oxygen flow to the affected lesion site, causing scar maturation to accelerate.⁸⁶ The localized hypoxia may also result in fibroblast degeneration and cell breakdown, which is beneficial in reducing recurrence of pathogenic scarring.^{223,284} In the absence of the superior surface pressure, the collagen fibres develop in a nonsystematic pattern and raised scarring can present²¹⁸. Pressure therapy devices should often, dependent on site be worn 24 hours a day for around a 12-18 months or until scar maturation occurs.¹⁷⁴ However, it is acknowledged that in some regions positive pressure splints can not be worn continuously (e.g., face) and in those instances compression therapy should aim to remain in place for 12 hours a day for a minimum 6-12 months.²⁸⁵ The exerted pressure should be at least 24 mm Hg, in order to exceed the inherent capillary pressure, but must not surpass 30 mm Hg to prevent peripheral circulation complications.^{86,168,286,287} Pressure adjuvant therapy often commences after wound re-epithelialization and suture removal at around 10-14 day²⁸⁴ and may reduce keloid scar formation by 70% when used consistently.⁸⁶ Side-effects are rare, but may include pressure ulcers.¹⁷⁴ Good patient education, including realistic expectations of compliance and success are key motivating factors for patient usage of pressure therapy.²⁸³ One RCT (LOE-2, Table 51-18 and its electronic version)⁹¹ was examined which evaluated pressure therapy alone against pressure therapy and SGS for the management of HT burn scars in two active treatment groups, for ethical reasons of withholding standard therapy no control group was included. This was a single blinded study with a good

(text continued on page 802)

TABLE 51-16—Monotherapy and Polytherapy Published Clinical Trials: Imiquimod Treatment Modality

Imiquimod	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Polytherapy</i>										
Martin-Garcia ¹⁶⁷	4	Comparative	Exc & imiquimod vs Exc & ILS	K	6 patients (Fitzpatrick skin type II-V) with bilateral earlobe K scars, excluded if pregnant, immunosuppressive, significant medical condition or previous treatment in last 3 months	Scar reoccurrence	Exc: parallel shave surgery, imiquimod cream applied daily for 8 hrs for 8 weeks to 1 st scar, ILS (TA 5 mg/mL); day 1, week 2, 4, 6, 8 to 2 nd scar	6 months (prospective)	+Exc & imiquimod (NS) > Exc & ILS	After 6 months 75% of the imiquimod group remained reoccurrence free. In comparison to the ILS group, 50% of the imiquimod treated scars remained clear of reoccurrence, while experiencing a re-growth in the ILS treated side. Local skin irritation secondary to imiquimod use required rest periods in 3 cases.
Cacao ²²⁴	4	Case-series	Exc & imiquimod	K	9 patients (various ethnicities) with stable trunk K lesions, excluded if active skin/systemic disease present, pregnant or using immunosuppressant drugs	Scar erythema, symptoms & size	Exc, imiquimod: daily from day 0 for 8 weeks	≤8 months (prospective)	-Exc & imiquimod (NS)	K scar reoccurred in 8 patients (7 after 12 weeks post surgery). Imiquimod 5% is not effective here in preventing reoccurrence of trunk K scars after surgical excision.
Stashower ²¹⁷	4	Case-series	Exc & imiquimod	K	4 patients (of various ethnicities) with 8 large earlobe keloids, excluded if received previous therapy or taken an immunosuppressive medication in last 6 months	Scar overall appearance, symptoms & size	Tangential shave Exc, imiquimod (5%); cream daily for 6 weeks	12 months (prospective)	+Exc & imiquimod (NS)	After 12 months no evidence of reoccurrence was noted in any lesion, the scars were asymptomatic and an excellent cosmetic result was achieved.

Berman ²²⁵	4	Case-series	Exc & imiquimod	K	12 patients (various ethnicities) with 13 K scars, ≥1 year old, excluded if previously treated in past 2 months, pregnancy, systemic or immune disorders	Scar erythema, edema, pigmentation, reoccurrence, symptoms & size	Exc, imiquimod: daily from day 0 for 8 weeks	6 months (prospective)	+Exc & imiquimod (NS)	No lesions reoccurred by 24 weeks (of the 11 evaluated). Hyperpigmentation side effects were high (64%). Reoccurrence rates of K scars treated with post-operative imiquimod here were lower than other published literature.
Malhotra ²²⁹	5	Case report	Exc & imiquimod	K	2 patients (Fitzpatrick skin type IV) with 3 presternal K scars	Scar reoccurrence	Exc: radio-frequency, imiquimod: cream applied daily overnight for 8 weeks	3 months (retrospective)	-Exc & imiquimod (NS)	No reoccurrences were seen while on imiquimod treatment, however, all K lesions reoccurred within 4 weeks of stopping the treatment.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGS, silicone gel sheet; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional cryosurgery; ILS, intralesional steroid; IL, intralesional; Exc, excision; ELExc, extralesional excision; ELEXc, extralesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate

TABLE 51-17 — Monotherapy and Polytherapy Published Clinical Trials: Mitomycin C Treatment Modality

Mitomycin C	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Polytherapy</i>										
Sanders ¹⁶⁶	4	Comparative	Exc & mitomycin C & vitamin A & C & ILS vs Exc & vitamin A & C & ILS	K	15 patients (majority African American descent) with ≥2 K scars in the head / neck region, no exclusion criteria stated	Scar overall appearance / reoccurrence	Exc: to 2 lesions (same patient), 1 wound treated with mitomycin C before skin closure, vitamin A&D ointment to each wound: 3/day for 7 days, ILS (TA 40 mg/mL): 1/month for ≤6 months	0-28 months (prospective)	-Exc & mitomycin C & vitamin A & C & ILS, +Exc & vitamin A & C & ILS (NS)	The study demonstrated no significant difference between K scars treated with Mitomycin C applied topically after excision in preventing re-occurrence in the same individual.
Talmi ²¹⁹	4	Case-series	Exc & mitomycin C	K	8 patients (?ethnicity or skin type) with various K scars, no exclusion criteria stated	Scar overall appearance, patient satisfaction & scar thickness	Exc & wound treated with single 5-FU treatment	≤14 months (prospective)	+Exc & mitomycin C (NS)	Mitomycin C following scar excision appears to be an effective treatment of K scars. All patients were satisfied with the results, although complete K disappearance was evident in only 2 patients at 2 months.
Stewart ²²⁰	4	Case-series	Exc & mitomycin C	K	10 patients (majority darker-skinned individuals) with head / neck K scars, no exclusion criteria stated	Scar overall appearance / reoccurrence	Exc & wound treated with single 5-FU treatment	≤14 months (retrospective)	+Exc & mitomycin C (NS)	Topical application of mitomycin C was found to be effective for the prevention of K scarring in the head and neck, with a success rate here of 90%.
Bailey ²²⁶	4	Case-series	Exc & mitomycin C	K	10 patients (various ethnicities) with a range of K scars, excluded if pregnant or planning to conceive	Scar overall appearance	Exc (shave-removed), mitomycin C: applied before skin closure (for 3 mins) & repeated after 3 weeks	6 months (prospective)	+Exc & mitomycin C (NS)	A satisfactory outcome was achieved in 80% of patients. This new treatment was effective in the majority of patients but further studies are needed to confirm the benefit.

RCT, randomized controlled trial, NS, not significant, +, positive, -, negative, SG, silicone gel, SGS, silicone gel sheet, SGC, silicone gel cushion, HT, hypertrophic, K, keloid, PDL, pulsed dye laser, IPL, intense pulsed light, SC, silicone cream, ?, no data found, CS, cryosurgery, ILCS, intralesional cryosurgery, IL, intralesional steroid, IL, intralesional, Exc, excision, ILExc, intralesional excision, ELEXC, extralesional excision, RXT, irradiation, 5-FU, 5-fluorouracil, IFN, interferon, MP, methylprednisolone acetate, TA, triamcinolone acetonide, BM, betamethasone sodium phosphate.

TABLE 51-18—Monotherapy and Polytherapy Published Clinical Trials: Pressure Treatment Modality

Pressure	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
<i>Monotherapy</i>										
Harte ⁹¹	2	RCT	Pressure therapy & SGS vs pressure therapy	HT	22 Caucasian patients with HT burn scars, excluded other scar types, presence of an infection or skin condition	Scar height, vascularity, pliability & pigmentation	Pressure therapy: pressure garment, SGS: applied under the garment for 23 hrs/day	6 months (prospective)	Pressure therapy & SGS = pressure therapy alone	No significant differences were established at 12 or 24 weeks between the two treatment groups, however both groups showed a general decrease in their group scar scores. Evidence here is inconclusive and a larger scale rCT is required.
<i>Polytherapy</i>										
Omranifard ¹⁴⁸	2	RCT	PDL vs ILS & pressure vs erbium laser	HT	120 patients (Fitzpatrick skin scale III) with HT scars ≥4cm long, <1 year old, excluded if received previous treatment within last 6 months	Scar pigmentation, vascularity, pliability & height	PDL/ILS (TA 5–10 mg/mL)/erbium:?: no. of treatments, every 4 weeks pressure therapy: garments	≤12 months (prospective)	+ILS & pressure < +PDL +erbium laser	All three groups significantly improved post treatment, but the results in the PDL and erbium laser treatment groups was significantly higher than the ILS & pressure group.
Harte ⁹¹	2	RCT	Pressure therapy & SGS vs pressure therapy	HT	22 Caucasian patients with HT burn scars, excluded other scar types, presence of an infection or skin condition	Scar height, vascularity, pliability & pigmentation	Pressure therapy: pressure garment, SGS: applied under the garment for 23 hrs/day	6 months (prospective)	Pressure therapy & SGS = pressure therapy alone	No significant differences were established at 12 or 24 weeks between the two treatment groups, however both groups showed a general decrease in their group scar scores. Evidence here is inconclusive and a larger scale rCT is required.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGS, silicone gel sheet; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCS, intralesional steroid; IL, intralesional; Exc, excision; ILExc, intralesional excision; EExc, extrallesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

description of the randomization technique. Pressure garments were tailor-made and worn for 23 hours a day, with silicone underneath dependent on therapy group. Scar assessment was completed using a validated form of the VSS and size measurements. No significant difference was established after 12 or 24 weeks of therapy.

Different types of polytherapy have been evaluated incorporating pressure therapy. The only additional RCT (LOE-2)¹⁴⁸ (described previously) supports the therapeutic role in combination with ILS, even though other modalities performed better. All level 4 evidence advocates the role of positive pressure treatment for the management of problematic scarring, for example after surgical excision alone,^{188,218} intralesional injections^{168,172} or a range of adjuvant therapies.^{85,86,168,174,176,177,201,221,223}

Others

Many other therapeutic options have been examined in the past twenty years in single and polytherapy studies, those that have been trialled as mono therapies are discussed individually here (Table 51-19 and its electronic version). Bleomycin is an antineoplastic agent, which has been used for other dermatologic conditions for many years, such as plantar warts. Bleomycin is not injected but instead dripped onto scars and the skin is then punctured to allow penetration through the dermis.^{133,288} In a comparative study (LOE-4),¹³³ bleomycin proved useful to therapeutically manage small lesions with similar results to CS and ILS but had significantly better results when treating large ($>100 \text{ mm}^2$) HT and keloid scars. Additionally, a case-series study (LOE-4)²⁸⁸ found equally positive results.

Calcipotriol has an anti-inflammatory influence, it actively stimulates keratinocyte differentiation, inhibits keratinocytes proliferation and suppresses the number of epidermal Langerhans cells and their antigen-presenting function.²⁸⁹⁻²⁹¹ One double-blinded RCT (LOE-2)²⁹¹ of 30 bilateral mammoplasty patients found that the application of topical calcipotriol to healing wounds did not prevent HT scar formation after 3 months therapy.

Research has demonstrated close links between tension levels and an increased scar tissue formation.^{183,292,293} Fibroblast mechanical tension induces signal transduction and cell proliferation, growth factor production and collagen synthesis.²⁹⁴ In particular longitudinal stretching, parallel to the axis of the wound stimulates the hypertrophic process.²⁹⁵ Atkinson (LOE-2)²⁹⁶ found that paper taping was effective at reducing scar tension and preventing the development of HT scarring when worn continuously for 12 weeks from day 4-6 postoperatively. This was a significant difference and those patients in the control group were 13 times more likely to develop raised scarring. However, this study was weakened by the large number of drop-outs and the lack of blinding for data collection, although quantitative ultrasound measurements were included. Other authors^{295,297} also found that control or elimination

of longitudinal stretching forces by long-term paper taping was an effective preventative treatment. Nevertheless, it must be noted that no untreated control scars developed hypertrophy in the Widgerow²⁹⁷ study either.

Occlusive dressings provide three main polytherapy components: scar support, hydration and light pressure therapy, all of which have been highlighted previously in the text.^{83,183,297} A number of studies have been examined which indicate that occlusive dressings alone provides equal,⁹⁶ better¹⁰⁷ or worse⁹⁷ results than similar SGS products. Philips (LOE-2)²⁹⁸ determined that hydration of keloids and HT scars by a hydrocolloid dressing resulted in statistically significant symptomatic improvement, but no change in physical scar parameters when compared to daily liquid moisturization. Although the study was small and no clear blinding or randomization was documented. Some evidence has reported that intralesional botulinum toxin (Botox) type A can relax muscle tension in a healing wound and could affect fibroblast cell cycle distribution in HT scars.²⁹⁹ Two studies (LOE-4)^{300,301} evaluated the effect of Botox type A. Three monthly injections were received and therapeutic satisfaction, erythema, symptoms and pliability were recorded. After 6 months, satisfaction was very high and all HT scar parameter were significantly improved, however no blinding was reported³⁰¹. Another smaller study (n=12)³⁰⁰ in keloid scars demonstrated peripheral regression in all lesions, decreased height and no recurrences after a year.

Tranilast (N-antranilic acid) is a selective inhibitor of collagen synthesis. This is available in an oral medication form but selective distribution into raised scar tissue is impossible. Therefore, when transdermal iontophoretic delivered tranilast was administered to HT and K scars, the results were more beneficial than oral treatment for relieving pain and itch³⁰². Pentoxifylline is a methylxanthine phosphodiesterase inhibitor and has been tested as a potential anti-fibrotic agent. It is reported to have a direct effect on inhibiting proliferation of burn scar fibroblasts and fibroblast-populated collagen lattice contraction^{303,304}. In clinical trials (LOE-4)³⁰⁴ it was noted that the extensibility and elasticity of scars can be increased with intralesional pentoxifylline.

Captopril has previously been demonstrated to be effective at preventing HT scar formation in animal studies by inhibiting angiotensin-converting enzyme in the skin, which could essentially suppress TGF-b1 and the release of interleukin-6. This can block fibroblast proliferation, collagen production and precipitate matrix metalloproteinase activity.³⁰⁵ When captopril 5% cream was applied to HT and keloid hand scars twice daily for 6 weeks, a 7mm reduction in scar height was noted and redness and itch were eliminated³⁰⁵. Other authors (LOE-2:1, LOE-4:5) have also examined and supported the use of scar massage¹²⁰, topical onion extract,^{73,162} additional vitamins A plus C¹⁶⁶, E⁷⁹ and other active extracts²⁹⁷ compounds as various forms of the multi-modal approach to scar management.

TABLE 51-19—Monotherapy and Polytherapy Published Clinical Trials: Other Treatment Modalities

Other	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Monotherapy										
Vander Veer ²⁹¹	2	RCT	Calcipotriol vs placebo	HT	30 female patients (?ethnicity or skin type) undergoing bilateral reduction mammoplasty, excluded if had a current/planned pregnancy in next year or post-operative complications (i.e. infection)	Scar overall appearance, thickness & biopsy sampling	Cream:10 days to 3 months post-operative, 2/day application	1 year (prospective)	-Calcipotriol (NS)	No significant difference was observed in the prevalence of HT scars treated with calcipotriol or placebo ointment. A strong association between keratinocytes activation and HT scar formation ($p=0.001$) was recorded.
Wigger-Alberti ¹⁰⁷	2	RCT	SGS vs poly-urethane dressing	HT	60 patients (?ethnicity or skin type) with HT scars $\geq 60\text{mm}$ long, extensive exclusion criteria including K scarring and other treatments in the last 2 months	Scar overall appearance, color, matte/shiny, contour, distortion & texture	SGS/dressing: 23-24 hrs/day for 3 months to half of scar	3 months (prospective)	+polyurethane dressing > +SGS	Both regimes demonstrated a significant reduction in the clinical HT scar signs over 3 months. However, the polyurethane dressing was significantly better at reducing the clinical signs at 4 and 8 week reviews and was tolerated more than the SGS.
Phillips ²⁹⁸	2	RCT	Hydrocolloid occlusive dressing vs moisturizer	HT & K	20 patients (?ethnicity or skin type) with existing long standing HT or K scars, no exclusion criteria stated	Scar size, volume, pigmentation, vascularity, pliability, height, symptoms & oxygen	Dressing: continuous for 8 weeks Moisturizer: 1/day application	3 months (prospective)	+Hydrocolloid occlusive dressing (NS) +Moisturizer (NS)	Itching significantly reduced ($p<0.03$), pain decreased ($p<0.08$) and pliability increased 10% for both treatment groups over 2 months. The authors proposed that an improved hydration may account for the symptomatic relief observed.

(Continued)

TABLE 51-19—Monotherapy and Polytherapy Published Clinical Trials: Other Treatment Modalities (Continued)

Other	LOE	Study Design	Evaluated Treatment	Scar Type	Participants	Primary outcome measure	Treatment regime	Assessment period	Outcome	Principal conclusions
Atkinson ²⁹⁶	2	RCT	Paper tape vs untreated control	HT	70(Caucasian) patients post caesarean section, excluded allergy sensitive to tape, developed post-operative wound complication, history of K scarring, had comorbidities or medication known to affect wound healing	Scar depth, size & volume	Tape: 12 weeks continuous treatment from day 4-6 post-operatively	6 months (prospective)	+Paper tape	Paper tape was an effective modality for the prevention of HT scarring by reducing scar tension. At 12 weeks there was a significant difference between treatment groups ($p=0.003$) and scar volume. Patients in the control group were 13 times more likely to develop a HT scar than the treatment group.
De Oliveira ⁹⁶	2	RCT	SGS vs placebo sheet vs untreated control	HT & K	26 patients (?ethnicity or skin type) with 41 HT or K scars, excluded if radiation or steroid therapy in previous 12 months, or lesion <3 months old	Scar size, coloured, induration & symptoms	Sheet: 24 hrs/day	4.5 months (prospective)	+SGS +placebo sheet	Significant reduction in parameters for silicone and control sheet groups compared to the control scars. No significant difference identified between silicone and control sheet groups.
Momenti ⁹⁷	2	RCT	SGS vs placebo sheet	HT	38 patients (?ethnicity or skin type) HT burn scars, excluded if wound infection, open wound or sensitivity to SGS	Scar pigmentation, vascularity, pliability & symptoms	Sheet:12-24 hrs/day	4 months (prospective)	+SGS	All scar parameters were significantly reduced in the SGS group in comparison to the control region after 4 months, except pain. For HT burn scars, SGS is an effective treatment.
Li-Tsang ¹²⁰	2	RCT	SGS & massage vs massage	HT	45 patients (Chinese ethnicity) with post-traumatic HT scars, no exclusion criteria stated	Scar thickness, pigmentation, height, vascularity, pliability & color	SGS:24hrs/day Massage: 15 mins/day for 6 months	6 months (prospective)	+SGS & massage > massage	Significant reductions in scar thickness at 2 and 6 months were noted in the SGS and massage group. Symptoms, pliability and pigmentation also improved with SGS and massage therapy.

<i>Polytherapy</i>									
Palmieri ⁷⁹	2	RCT	SGS vs SGC with added vitamin E	HT & K (?ethnicity or skin type) with HT and keloid scars, no exclusion criteria stated	Scar symptom, color, size & cosmetic appearance	Sheet:10 hrs/ night	2 months (prospective)	+SGC with vitamin E (NS)	SGC with added vitamin E scored better than simple SGS at both 1 and 2 month periods studied
Sawada ⁷⁵	2	RCT	SC with light dressing vs SC with occlusive dressing vs placebo with occlusive dressing	HT & K (?ethnicity or skin type) with HT or K scars, excluded if infected or ulcerated scars	Scar redness, elevation, hardness, itching & symptoms	Cream: 1-2 times/day	3-5 months (prospective)	+SC with occlusive dressing > SC with light dressing	Statistically significant improvement in the SC and occlusive dressing group compared to the SC and light dressing group, with an improvement in redness, tenderness, itching and hardness recorded.
Li-Tsang ¹²⁰	2	RCT	SGS & massage vs massage	HT	45 patients (Chinese ethnicity) with post-traumatic HT scars, no exclusion criteria stated	Scar thickness, pigmentation, height, vascularity, pliability & color	SGS:24hrs/ day Massage: 15mins/day for 6 months	+SGS & massage > massage	Significant reductions in scar thickness at 2 and 6 months were noted in the SGS and massage group. Symptoms, pliability and pigmentation also improved with SGS and massage therapy.

RCT, randomized controlled trial; NS, not significant; +, positive; -, negative; SG, silicone gel; SGS, silicone gel sheet; SGC, silicone gel cushion; HT, hypertrophic; K, keloid; PDL, pulsed dye laser; IPL, intense pulsed light; SC, silicone cream; ?, no data found; CS, cryosurgery; ILCs, intralesional cryosurgery; ILs, intralesional steroid; IL, intralesional; Exc, excision; ILExc, intralesional excision; ELExc, extrallesional excision; RXT, irradiation; 5-FU, 5-fluorouracil; IFN, interferon; MP, methylprednisolone acetate; TA, triamcinolone acetonide; BM, betamethasone sodium phosphate.

DISCUSSION

Keloid and hypertrophic scarring continue to be a challenge for healthcare providers. A wide range of potential treatment approaches and combination therapies have been proposed in the published literature with variable results. Despite the recent advances, a number of current therapeutic modalities for managing dermal scars can be ineffective, costly, and inconvenient, prove painful and have undesirable side-effects^{59,306}. There is therefore, a significant need for further RCT and quantitative systematic analysis of available scar therapies⁶⁰. Many studies examined to date appear to have been poorly designed thus making it difficult to derive conclusions regarding the reliability and transferability to daily clinical practice.

The vast majority of published research in the last twenty years, 116/173 (67%) studies have provided level 4 evidence and only 31 studies were LOE-2 and 10 studies were LOE-3. Treatment comparisons were difficult due to a number of study design flaws. The degree of scar heterogeneity in each single study was poorly controlled, with varying scar ages, types, various scar locations and inconsistencies in reported patient ethnicities^{113,147,166,177}.

Scarring is an individual process; no two scars present or develop the same, even in the same individual with the same exact scar type and age, therefore the extent to which these can be reliably compared is questionable. It is preferable that scar modulation modalities are compared within the same scar under similar external effects (e.g., skin tension and physiologic movement) in separate regions. Although it is acknowledged that this is the ideal and would be perhaps better suited to HT scars which are uniform by nature than keloid lesions. A quantitative assessment of scars using objective measurement tools will be of use in comparing different scars and treatment modalities. Recruitment of large patient numbers with a suitable level of homogeneity may take time especially in a single-site study. Hence, a multisite collaborative approach is likely to be of benefit and this may require significant additional resources and provision of adequate infrastructure³⁰⁷.

Despite the well-defined clinical characteristic differences between HT and keloid scarring, frequently there appears to be misdiagnosis and differences between studies of what is considered a keloid and a HT scar. It is therefore important that future studies would employ clear diagnostic guidelines in the assessment of raised dermal scarring in order to generate uniformity and homogeneity in case selection. Some scars however may be better defined as intermediate lesions as clinically they appear in between keloids and HT scars, this further exemplifies the need for development of an improved scar classification system^{55,60,61,308}.

The long-term follow-up of scar patients is essential, not only to simply determine the overall positive or negative treatment outcome but also to determine the effects

of stopping a treatment intervention. A criticism of many studies reported here was their short duration (less than 1 year) as early outcome measurement is likely to miss a late recurrence. Therefore, treatments evaluated as effective during these short-term studies needs to be viewed with caution. Some authors have acknowledged that when keloid scar therapy was stopped the lesions began to grow again²⁷⁹. Furthermore HT scars may take 2-5 years to mature^{27,60} and therefore even in a long-term follow-up trial, the question can be posed - whether the authors are evaluating the treatment or the natural scar evolution? Length of follow-up may also become more important in the future as healthcare providers look to potentially only fund treatments, which have proven and established long-term efficacy and cost-effectiveness.^{309,310}

In the literature reviewed, there is a need to standardize scar treatment protocols in order to evaluate each treatment at a baseline level. From which, new emerging therapy can be methodically trialled to establish the potential benefit to patients with scars non-compliant to currently available treatments.⁵⁷ Many studies also demonstrate a lack of randomization or they may state that they are randomized but do not provide sufficient details of the technique or the allocation of concealment^{102,144}. For example, the efficacy of silicone products was deemed unclear by the Cochrane Collaborative¹⁰⁵ because of poor study design and a high susceptibility to bias. Studies should recognize and relate their research findings to the Consolidated Standards of Reporting Trials (CONSORT)³¹¹ guidelines to enable transparency documentation of clinical research findings.

There were also a limited number of double-blinded studies for the management of keloid and HT scars. This may be caused by poor initial trial design, limited time, financial resources or a combination of both cannot be fully ascertained here. Placebo treatments are not impossible and could include intralesional saline injections, sham RXT or low-energy laser, which would not be expected to have any clinical effects.⁵⁵ Patient blinding is also important because for example in topical therapy studies, there is a psychological impetus to apply a believed 'active' cream or therapy to both sides or scars which can only be diminished with true placebo blinding. Throughout the normal continuum of tissue repair the resultant scar matures and evolves therefore quantitative analysis is empirically important due to the significance of the ill-defined treatment of raised skin scarring despite the range of therapeutic modalities and high recurrence rates.³¹² Assessments of efficacy need to be standardized and validated in the specific scar group they are being used to evaluate such as the MSS,⁴² VSS,¹¹⁴ Patient and Observer Scar Scale.³¹³ Subjective tools express an overall scar consensus, relying on the personal evaluation by the rater and often the patient. This personal perspective can be manipulated by prejudiced due to many external factors including feelings, beliefs and desires of the individual involved.³¹⁴ Hence it is critical in clinical

evaluation and especially research trials that quantifiable objective measurements are sort to validate treatment efficiency. True objective scientific evaluation encompasses biochemical and histological analysis involving invasive biopsy sampling which results in destruction of the scar under investigation.³¹⁵ Therefore this method has a limited application to the clinical scar population and hence non-invasive techniques are recognized as more

favorable to scar sufferers but can have the tendency to be less quantifiable than invasive methods.³¹⁶ At each stage of this advancement non-invasive objective assessment tools can be utilized to monitor erythema, vascularity, hypertrophy, contracture, flexibility and the overall scar dimensions. This repeated examination process is critical if modulatory therapies are to be appraised rigorously⁶² (Figure 51-7).

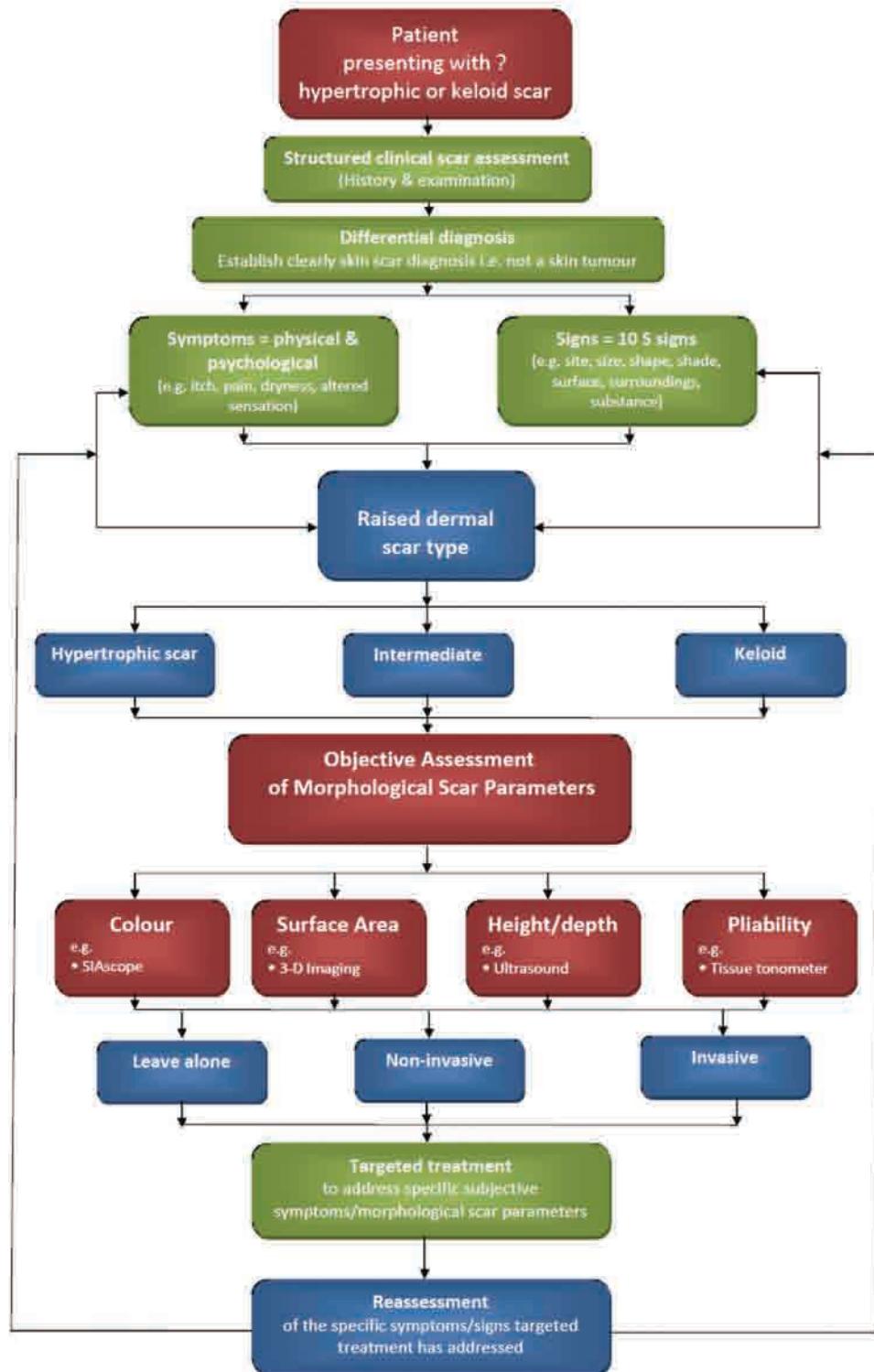


FIGURE 51-7 Flow-chart of the scar assessment process (as practised by the senior author).

In addition, studies evaluated here frequently assessed the outcome parameter of 'scar recurrence' but no clear definition of this subjective parameter was defined^{166,220}. Furthermore if recurrence is inevitable in some severe keloid lesions and the patient accepts this then perhaps a particular 'control' level should also be defined to characterize a 'successful' treatment.^{219,226} This may also relate to more specific therapeutic goals to be achieved depending on the requirements of the patient, for examples cosmesis, function or symptom management. These aspects have been previously suggested to be examined as independent endpoints by some authors.⁵⁵ This standardization of study design practices is essential to the development of quality studies, which can facilitate effective modality cross-comparisons and fundamentally enable meta-analyses to be completed. In the United Kingdom, the National Institute of Health Research (NIHR)³¹⁷ has set up a network of Research Design Services and Local Research Networks to assist clinicians and clinical researchers by providing access to key professional advice to strengthen the quality of new research undertaken and improve applications for government funding. The NIHR national databases may also assist in multi-center collaborations by effectively 'advertising' a study to other interested clinicians.

Advice Based on Current Understanding Scar Formation and Existing Literature

The control and modification of the inflammatory process post dermal injury may decrease raised scar formation. Several treatment modalities exist which can inhibit the inflammatory cascade at different levels, therefore a polytherapeutic approach may diminish scar formation.⁵⁸ However, it must be remembered that skin scarring is often a process, which requires long-term management. It is important that the patient understands the long-term nature and the duration of any treatment administered. In order to ensure compliance and adherence to any treatment regime, it is also important to assess the patient's psychological status before and during the treatment. The ability to commit to any treatment will determine potential response and prognosis and avoid disappointment in high expectation of scar eradication at an early stage (Table 51-20). Following examination of the data presented here, it seems that raised dermal lesions of small dimensions may benefit from intralesional therapy, primarily steroids that are administered via a full course of regular injections over a period of time (current advice is 4 weekly injections until full resolution unless contraindicated). If they fail to improve after a trial period of at least three to 6 months then surgery may be suitable. All surgery of raised dermal scars should be followed up and receive postsurgical adjuvant therapy. The role of neoadjuvant treatment is unclear. It would appear to be beneficial to offer ILS, SGS and pressure therapy post-surgery. Post-excisional radiation

TABLE 51-20

1. The presence of positive family history
2. Previous poor response
3. Multiply recurrent scar
4. Specific anatomical locations (e.g. sternum)
5. Large scar size
6. Irregular, non-geometric scar morphology
7. Prolonged active inflammation
8. Severe symptoms (e.g. tenderness, constant itching)
9. Psychological
10. Social history

appears to be more effective for larger, more severe and resistant lesions and laser therapy may benefit erythematous and symptomatic scars. Occlusive dressings or SGS should be applied early after surgical procedures to reduce hypertrophy and provide dermal support. If occlusive dressings are not used, paper taping may also be beneficial but this must stay in place as long as possible (minimum six weeks) to prevent the negative side-effects of disrupting the permeability barrier, increased transepidermal water loss which can potentially increase scarring⁸¹. There is limited study data for the inclusion of other therapeutic modalities such as IFN, verapamil and mitomycin C. All appear promising areas for further clinical research prior to regular clinical use. Rigorous high quality RCTs (LOE-1) are needed to evaluate these existing therapeutic options, which are currently in wide-scale use without underpinning evidence-base. Other well-designed trials such as large non-randomized controlled studies (LOE-2) and prospective cohort studies (LOE-2) can also significantly increase the quality of available literature.

CONCLUSION

There is a significant lack of existing high quality research for the evaluation of therapeutic management options undertaken in keloid and HT scarring. In the last 20 years, available literature is predominantly classified as level 4 evidence only. A combination of factors appears to have subsequently led to the low quality available research pool at present to base current and future treatment upon. Improved methodological and analytical reporting by authors, in conjunction with an increased compliance of trial reporting guidelines and developments in government health research support services may improve future study design quality.

However, future studies must primarily address the heterogeneity of scarring and the continuum of dermal scar types through an amalgamation and consensus approach. This will undoubtedly require a new sub-classification of both hypertrophic and keloid scars to be developed which bridge-the-gap between the genetic, morphologic, immunohistochemical and clinical characteristics widely observed.

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Treatment of Acne (Non-Medical Interventions)

52

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INTRODUCTION

Acne is a disease of the pilosebaceous unit characterized by development of both inflammatory and/or noninflammatory lesions that may ultimately result in scarring. The lesions may present as comedones, inflammatory papules, pustules, nodules, and cysts. Four factors are thought to contribute to this multifactorial disease: follicular hyperproliferation with subsequent follicular plugging; excess sebum production; the presence and activity of *Propionibacterium acnes*; and inflammatory response of the tissue. With its conspicuous cosmetic concerns and potential for scarring, acne may frequently have a profound psychological impact on the patient.

EPIDEMIOLOGY

Acne vulgaris is the most commonly occurring dermatologic disease worldwide. In the United States, 60-70% of the population is affected by acne at some point of life.¹ Persons of certain races are affected more than others. The Mediterranean region from Spain to Iran has high prevalence of cystic acne.² During adolescence, acne is more common in males than in females. In adulthood, acne vulgaris is more common in women than in men.³

Rarely, acne vulgaris may affect newborns in the first few weeks of life because of the presence of maternal hormones and the resultant excessive sebum production. The neonate may have small papules and impacted follicles, which may require topical retinoids for clearance; however, this transient condition usually resolves spontaneously.

ETIOLOGY AND DIAGNOSIS

The etiology of acne, as already mentioned, is multifactorial. Along with the four main factors believed to be involved in acne causation, there are new etiologic factors found to be contributory. All the factors are enumerated as below:

- Genetics- The inherited factors that lead to transfer of acne from one generation to the next is the propensity for follicular epidermal hyperproliferation and

subsequent plugging of the follicle.⁴ It is also believed that the size and number of sebaceous glands and their activity level appear to be inherited. The inheritance may not be evident in each generation and skipping of generations is commonly observed. An autosomal dominant pattern of inheritance is suggested, but the high prevalence of acne in general may limit the attribution to this genetic component.

- Retention hyperkeratosis- In individuals with acne, follicular epithelium produces cells at a very rapid rate and these cells are retained leading to plugging of follicles.⁵ It is believed that increased corneocyte cohesiveness also contributes to this accumulation of cells and follicular obstruction.
- Excessive sebum production- Hormones, especially androgens and other chemical mediators, play the key role in modulating sebum production and release.⁶ Around the time of adrenarche, follicular plugging begins to appear in patients with acne. The levels of adrenal androgen and dehydroepiandrosterone sulfate (DHEAS), in prepubertal girls can be correlated to the severity of acne.⁷ Despite normal levels of androgens, both males and females may still develop acne, for which a sebaceous gland hyper-responsiveness to androgens has been proposed.
- Peroxisome proliferator-activated receptors (PPAR) also partly regulate sebum production. Ottaviani et al. demonstrated the possible involvement of lipid peroxides, in particular squalene peroxides, in establishing an inflammatory process in acne.⁸

What is the mechanism by which *Propionibacterium acnes* causes acne?

Propionibacterium acnes (*P. acnes*) is a normal commensal bacteria of the skin, which colonizes the occluded pilosebaceous units. It breaks down the trapped sebum into free fatty acids and peptides triggering an inflammatory response mediated by proinflammatory mediators, which diffuse through the follicle wall. *P. acnes* is also known to activate toll-like-receptors (TLR) on monocytes and neutrophils which leads to the production of proinflammatory cytokines such as interleukins (IL)-12, IL-8 and

tumor necrosis factor (TNF).⁹ Alternatively, it is possible that some individuals are hypersensitive to *P. acnes* and develop an inflammatory response while others do not.¹⁰ Similar to a type IV hypersensitivity reaction, keratinocyte hyperproliferation and acne development seem to be initiated by up-regulation of interferon 1 alpha.¹¹ This is mainly because of the relative deficiency of linoleic acid caused by excess sebum and altered follicular barrier function. This results in production of cytokines that stimulates local endothelial cells, up-regulating inflammatory vascular markers such as E-selectin, vascular cell adhesion molecule-1 (VCAM-1), intercellular adhesion molecule-1 (ICAM-1), and human leukocyte antigen-DR (HLA-DR) in the perifollicular vasculature of the pilosebaceous unit.

Molecular genetic studies have led to complete sequencing of *P. acnes* genome, which has shown to include lipases. It has been suggested that one function of the *P. acnes* lipase may be to aid colonization within the pilosebaceous follicle by promoting cell adherence to components such as oleic acid.¹² In addition, lipases may help *P. acnes* to breakdown sebum, heat shock proteins that lead to cytokine production, and inflammation. Additional *P. acnes* enzymes increase porphyrin production, which subsequently induces neutrophil chemokine production and accelerated oxidation of squalene in the sebum leading to comedogenesis.

The inflammatory cytokines act on their respective receptors through autocrine and paracrine mechanisms and amplify the signals that activate the activator protein (AP)-1 transcription factor. This further induces matrix metalloproteinase (MMP) genes, the products of which degrade and alter the dermal matrix.¹³ These MMPs include collagenases, gelatinases, stromelysins, and matrilysins.

CONCLUSION

P. acnes acts on sebum, releasing free fatty acids and peptides, which trigger inflammation in the follicle by means of several receptors and mediators.

What is the biofilm hypothesis and what is its importance in acne?

In the pathogenesis of *P. acnes*, a biofilm hypothesis has been proposed, which has suggested that bacteria residing within the follicles actually grow as a biofilm. These biofilms consist of an aggregate of bacterial microorganisms, which grow within an extracellular polysaccharide substance. Although *P. acnes* biofilms have not been observed directly in the pilosebaceous unit, it has been shown that *P. acnes* readily forms a biofilm in vitro as well as on various medical devices in vivo. In addition, sessile *P. acnes* demonstrate high levels of resistance, increased production of virulence factors, and quorum-sensing molecules which lend further

support to this hypothesis.¹⁴ The extracellular matrix consisting of lipoglycans and polysaccharides may provide a protective barrier against host defenses.¹⁵

CONCLUSION

Biofilm hypothesis has a role to play in acne development and while developing newer therapies of acne, this concept should be considered.

Do fats, chocolate and dirt increase acne?

Fatty acids are commonly thought to cause acne, and thus studies have been done to find their role in acne aggravation. Simopoulos et al.¹⁶ demonstrated that the ratio of omega-6 to omega-3 fatty acids in Western diets is commonly 10:1, while that in Japan is 4:1 and 2:1 in ancient civilizations. Omega-6 fats are proinflammatory mediators and are increased in inflammatory acne¹⁷ and high levels omega-3 fats have been shown to lower inflammatory markers.¹⁸

Chocolate consumption increases blood lipid levels and can supposedly lead to sebum production which is "less fluid" in consistency. This may be the reason for subsequent pilosebaceous follicle obstruction, follicle rupture, and inflammatory changes. Studies by Anderson and Grant¹⁹ and another by Anderson²⁰ have been conducted to understand the association between acne and cocoa intake. Unfortunately, these studies are limited by their lack of control groups and quantitative statistical analyses. Fulton et al.²¹ tried to overcome these limitations in their study but their findings could not conclusively establish an association.

Decrease in perspiration can reduce the growth of *P. acnes*.²² One small pilot study by Short et al. demonstrated a trend toward an increase in truncal acne lesion counts in the individuals from the exercising group.²³

The common misconception that dirt causes acne can cause people to wash too much or too often, which may actually worsen acne because of irritation of acne-prone skin. In addition, excessive washing can stimulate sebaceous glands to produce more oil resulting in more acne breakouts.

CONCLUSION

Although there have been a variety of hypothesis proposed, there is currently insufficient evidence to clearly demonstrate a role of chocolates and high fatty diets in the development of acne. Additionally, patients must be advised that there is a common misconception that dirt causes acne to develop. It is important to clarify this notion to prevent excessive or vigorous washing, which actually can worsen the irritation and even increase sebaceous gland production.

What is the role of IGFs and diets with high glycemic index in the development of acne?

Besides androgens, insulin like growth factors (IGF) that regulate the activity of the sebaceous glands may also contribute to acne formation.²⁴ Acne is proposed to be an IGF-1-mediated disease with smoking and diet believed to increase the insulin/IGF1-signalling. In human skin appendages, the strongest expression of IGF-1 protein was found in maturing sebocytes and suprabasal cells of sebaceous ducts.²⁵ A correlation between the mean facial sebum excretion rate and serum IGF-1 levels has been demonstrated in postadolescent acne patients.²⁶ Interestingly, metformin treatment and diets low in milk protein content and glycemic index seem to reduce this increased IGF-1 signaling. Persistent acne in adulthood with high IGF-1 levels may be considered as an indicator for increased risk of cancer, which may require appropriate dietary intervention as well as treatment with insulin-sensitizing agents.²⁴

Diets rich in carbohydrates with a high glycemic index have been implicated in aggravation of acne. This is mediated through the associated hyperglycemia, reactive hyperinsulinemia and increased formation of IGF-1. Conversely, diets with low glycemic load have shown to decrease serum IGF-1 levels and significantly improved acne in 12 weeks.²⁷ In addition, western diets in general have a high glycemic index. The low glycemic diets and lack of consumption of dairy products in 1200 Kitavan islanders of Papua New Guinea and 115 Aché hunter-gatherers of Paraguay are believed responsible for the absence of acne cases altogether in this population.²⁸ Skim milk consumption and acne have also been related and a strong association between intake of skimmed milk and acne was demonstrated in boys.²⁹ In fact, cow's milk has shown to contain high levels of IGF-1 even after pasteurization, homogenization and digestion. Due to the homology of the amino acid sequence between bovine and human IGF-1, the bovine IGF-1 can bind to human IGF-1 receptor and produce the same effects as human IGF-1.³⁰ Milk consumption increases circulating IGF-1 by 10-20% in adults and by 20-30% in children. In addition, it raises the ratio of IGF-1/IGF binding protein-3 making IGF-1 more bioavailable.

High saturated fat diets may also increase IGF-1 levels and low fat and high fiber diets decrease the concentration of IGF-1³¹ and androgens³² and increase concentration of sex hormone-binding globulin (SHBG).

CONCLUSION

Diets with increased glycemic index can cause increased activity of sebaceous glands by production of IGFs. There is some evidence that milk may increase acne.

SEARCH METHODOLOGY

The search methodology for compiling this chapter comprised of articles and reviews from Pubmed central,

Medscape, and emedicine online. For gathering information regarding procedures, multiple textbooks were referred.

MANAGEMENT

Chemical Peels:

Table 52-1 is an evidence based table summarizing the non-medical modalities used in management of acne. Table 52-2 presents a **Strength of Recommendation for these modalities**.

Are chemical peels effective in treatment of acne?

Chemical peels constitute nonlaser therapeutic options for superficial exfoliation. They aid in hastening the process of resolution of comedones by their transition to superficial epidermis, which otherwise takes between 2-6 weeks to resolve.³³ Chemical peels because epidermolysis of the stratum granulosum layer and the degree of this effect depends on the pH and the concentration of the product used.^{34,35} This results in improved elasticity of stratum corneum as new cells are produced and stimulate collagen production in superficial dermis.³⁵

The most commonly used chemical peel is glycolic acid, an alpha-hydroxy acid, which is available as a facial wash and can be used at home or in the office for procedures performed by the dermatologist. As discussed above, the patient's acne preferably should be of comedonal type and patients should not be on oral retinoids, as this may aggravate the irritation with the peels. In patients with no current medical acne regimen, appropriate topical antibiotic and /or topical retinoid should be supplemented. With the glycolic acid peel, the aim is to penetrate down to the stratum granulosum layer, indicated by "frosting" of the skin, achieved 2 and 10 minutes after application. This implies epidermolysis and detachment from the papillary dermis.^{36,37} The acid is then neutralized with a buffered bicarbonate solution or cool water to prevent any deeper peeling. Atzori et al. demonstrated the efficacy of the glycolic acid peel in a study by on 80 females undergoing 70% glycolic peels every 10 days for six or more treatments.³⁸ The most rapid improvement was observed in comedonal acne. In papulo-pustular forms, an average of six applications was necessary. Although nodular-cystic forms required eight to ten applications, a significant improvement of the coexisting postacne superficial scarring was noted. The procedure was well tolerated and patient compliance was excellent.

Salicylic acid peels are performed as in-office procedures with 20% to 30% concentration and for home use with concentration 0.5% to 10%.³⁹ Although the regimen is very similar to that used for glycolic acid, salicylic acid precipitates on the skin, leaving behind the white frost to

TABLE 52-1—Evidence Based Table for Various Non-Medical Interventions in the Treatment of Acne Vulgaris

Investigators	Objective	Methods	Results/Conclusions	Level of Evidence
Chemical Peels				
Ilknur et al ¹	To compare the therapeutic effects of glycolic acid (GA) peels and amino fruit acid (AFA) peels in patients with acne vulgaris	Single-blind, randomized, right-left comparison study, 24 patients received 12 serial peels (GA and AFA, at concentrations from the lowest to the highest) on the two halves of the face at 2-week intervals for 6 months	There was a statistically significant decrease in the number of non-inflamed lesions with GA following the first month and with AFA following the second month ($p < 0.05$). The decrease in the number of inflamed lesions was statistically significant with GA at the end of the fifth and sixth months and with AFA only at the end of the fifth month ($p < 0.05$). When the two applications were compared with each other, there was not a statistically significant difference in terms of non-inflamed and inflamed lesions ($p > 0.05$). Compared to a GA peel, an AFA peel was less irritating and better tolerated.	2B (due to single blinding-low quality RCT)
Kessler et al ²	To compare the efficacy of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris.	Twenty patients were recruited in this split-face, double-blind, randomized, controlled study. An alpha-hydroxy acid (30% glycolic acid) was applied to one-half of the face and a beta-hydroxy acid peel (30% salicylic acid) was applied contralaterally every 2 weeks for a total of six treatments. A blinded evaluator performed quantitative assessment of papules and pustules.	Both the chemical peels were significantly effective by the second treatment ($p < .05$) and there were no significant differences in effectiveness between the two peels. At 2 months post-treatment, the salicylic acid peel had sustained effectiveness. More adverse events were reported with the glycolic acid peel after the initial treatment.	1B
Microdermabrasion				
Lloyd JR ³	To evaluate the use of microdermabrasion for the treatment of acne	Twenty-five patients with grade II-III acne received eight microdermabrasion treatments at weekly intervals. All patients were under dermatologic care and were maintained on their acne medications throughout the study.	Thirty eight percent (9/24) of the 24 patients who completed the study demonstrated excellent results, 34% (8/24) good results, 17% (4/24) fair results, and 12% (3/24) poor results. Ninety-six percent (23/24) of patients were pleased with their peer results and would recommend this procedure to others.	2B
Karimipour et al ⁴	To review the relevant literature and to evaluate the clinical efficacy of microdermabrasion in skin care.	Used an evidence-based approach	Role of microdermabrasion in acne is very limited.	2A
532 nm KTP Laser				
Baugh and Kucaba ⁵	To study the safety and efficacy of the potassium titanyl phosphate (KTP) 532 nm pulsed laser for the treatment of acne vulgaris.	Twenty-six subjects, clinically evaluated with moderate facial acne, were enrolled in this single-center prospective trial. The entire facial area for each subject was divided in half and randomly designated as either a treatment or a control side. Each subject was treated with four laser exposures using a KTP 532 nm laser with continuous contact cooling.	Primary outcome analysis in the Michaësson acne severity score demonstrated a mean 34.9% ($p = .011$) and 20.7% ($p = .25$) reduction at the 1-week and 4-week post-final treatments, respectively. Subjective investigator evaluations of overall percent satisfaction indicated that all patients demonstrated a minimum 50% overall satisfaction in treatment outcomes at the 4-week follow-up period. No side effects were encountered.	2B

(Continued)

585 nm Pulsed Dye Laser			
Leheta ⁶	To evaluate the role of the pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities.	Forty-five patients were randomly divided into three groups: group A received treatment with pulsed dye laser therapy every 2 weeks, group B received topical preparations and group C was subjected to chemical peeling using trichloroacetic acid 25%.	At 12 weeks of treatment, there was a significant improvement of the lesions within each group with the best results seen in group A; however, no significant difference was detected between the three treatment protocols after the treatment period. Remission in the follow-up period was significantly higher in the first group.
Karsai et al ⁷	To assess the efficacy of an adjuvant PDL treatment when combined with a proven topical treatment [fixed-combination clindamycin 1%-benzoyl peroxide 5% hydrating gel (C/BPO)].	Eighty patients (38 males and 42 females) were randomized in a 1:2 ratio to receive C/BPO alone or in combination with PDL treatment (wavelength 585 nm, energy fluence 3 J cm(-2), pulse duration 0.35 ms, spot size 7 mm).	Both groups showed a significant improvement during observation [Investigator's Static Global Assessment (ISGA) 27.1% (C/BPO) and 24.6% (C/BPO + laser), total lesion count 9.2% and 9.0%, inflammatory lesion count 36.3% and 36.9%, Dermatology Life Quality Index (DLQI) 54.5% and 42.5%], but there was no significant or otherwise appreciable difference between treatment modalities as far as the extent of improvement was concerned. Patients with more severe findings at baseline had a greater benefit from either therapy regimen.
Jung et al ⁸	To compare the efficacy and safety of PDL and of combined 585/1,064-nm laser treatment for mild to moderate facial acne in a randomized, prospective, split-face, double-blind study.	Sixteen participants with mild to moderate acne were treated with a single pass of a combined 585/1,064-nm laser on half of the face and PDL on the other half during each treatment session. Patients underwent three treatment sessions at 2-week intervals and were followed up at 8 and 12 weeks after treatment commencement.	At the final visit, inflammatory acne lesions were reduced by 86% on the PDL sides and by 89% on the 585/1,064-nm laser sides. Noninflammatory acne lesions showed corresponding reductions of 69% and 64%, respectively. A significant difference between the two treatments was observed for noninflammatory acne lesions at the eighth week. Histopathologic examinations showed that both treatments decreased inflammation and interleukin-8 expression and increased transforming growth factor beta expression.
Seaton et al ⁹	To compare the efficacy and tolerability of such PDL treatment with sham treatment in patients with facial inflammatory acne in a double-blind, randomized controlled trial.	Forty-one adults with mild-to-moderate facial inflammatory acne. We randomly assigned patients to PDL (n=31) or sham treatment (n=10). Treatment was given at baseline and patients were seen after 2, 4, 8, and 12 weeks.	After 12 weeks, acne severity (measured by Leeds revised grading system) was reduced from 3.8 (SD 1.5) to 1.9 (1.5) in the PDL group and 3.6 (1.8) to 3.5 (1.9) in the sham group ($p=0.007$). Treatment was well tolerated. Total lesion counts fell by 53% in PDL patients and 9% in controls ($p=0.023$), and inflammatory lesion counts reduced by 49% in PDL patients and 10% in controls ($p=0.024$).
Orninger et al. ¹⁰	To evaluate the clinical efficacy of pulsed dye laser therapy in the treatment of acne in a randomized, single-blind, controlled, split-face clinical trial.	Forty patients aged 13 years or older with facial acne received 1 or 2 nonpurpuric pulsed dye laser treatments to half of the face (fluence of 3 J/cm ²), serial blinded clinical assessments (lesion counts), and grading of acne severity using standardized bilateral serial photographs.	After 12 weeks, there were no significant differences between laser-treated and untreated skin for changes in mean papule counts (-4.2 vs. -2.2 ; $P=.08$), mean pustule counts (0 vs. -1.0 ; $P=.12$), or mean comedone counts (2.9 vs. 1.6 ; $P=.63$). Grading of serial photographs confirmed the clinical assessments, showing no significant mean differences in Leeds scores (range, 1-12) for treated skin (3.98 [0.32] at baseline and 3.94 [0.27] at week 12) compared with untreated skin (3.83 [0.32] at baseline and 3.79 [0.28] at week 12) ($P>.99$).

TABLE 52-1—Evidence Based Table for Various Non-Medical Interventions in the Treatment of Acne Vulgaris (Continued)

Investigators	Objective	Methods	Results/Conclusions	Level of Evidence
Visible Light				
Papageorgiou et al. ¹¹	To evaluate the use of blue light (peak at 415 nm) and a mixed blue and red light (peaks at 415 and 660 nm) in the treatment of acne vulgaris in a	One hundred and seven patients with mild to moderate acne vulgaris were randomized into four treatment groups: blue light, mixed blue and red light, cool white light and 5% benzoyl peroxide cream. Subjects in the phototherapy groups used portable light sources and irradiation was carried out daily for 15 min.	After 12 weeks of active treatment a mean improvement of 76% (95% confidence interval 66-87) in inflammatory lesions was achieved by the combined blue-red light phototherapy; this was significantly superior to that achieved by blue light (at weeks 4 and 8 but not week 12), benzoyl peroxide (at weeks 8 and 12) or white light (at each assessment). The final mean improvement in comedones by using blue-red light was 58% (95% confidence interval 45-71), again better than that achieved by the other active treatments used, although the differences did not reach significant levels.	1B
Goldberg and Russell ¹²	To assess the efficacy of this combination phototherapy	Twenty-four subjects, Fitzpatrick skin types II-V, with mild to severe symmetric facial acne vulgaris were recruited for the study. Subjects were well matched at baseline in terms of both age and duration of acne. Subjects were treated over eight sessions, two per week 3 days apart, alternating between 415 nm blue light (20 minutes/session, 48 J/cm ²) and 633 nm red light (20 minutes/session, 96 J/cm ²) from a light-emitting diode (LED)-based therapy system. Patients received a mild microdermabrasion before each session.	At the 4-week follow-up, the mean lesion count reduction was significant at 46% ($p=0.001$). At the 12-week follow-up, the mean lesion count reduction was also significant at 81% ($p=0.001$). Side effects were minimal and transitory. Comedones did not respond as well as inflammatory lesions.	2B
Na and Su ¹³	To assess the efficacy of red light phototherapy with a portable device in acne vulgaris in a split-face randomized-controlled single-blinded trial	Twenty-eight volunteers with mild-to-moderate acne were enrolled. The right or left side of the face was randomized to treatment side and phototherapy was performed for 15 minutes twice a day for 8 weeks.	The percent improvement in noninflammatory and inflammatory lesion counts of the treated side was significant compared to the control side ($p<.005$). Visual Analog Scale decreased from 3.9 to 1.9 on the treatment side and the difference between the treatment and control sides was significant at week 8 ($p<.005$), suggesting that red light has the potential for being used as a single treatment for acne.	2B
1450 nm Diode Laser				
Jih et al ¹⁴	To evaluate the dose response of a 1450-nm diode laser for treatment of facial acne, sebum production, and acne scarring utilizing two laser fluences and to determine long-term remission after laser treatment.	Twenty patients (Fitzpatrick skin phototypes II-V) received 3 treatments using the 1450 nm diode laser (3-4 week intervals). Split face comparisons were performed by randomizing patients to one of two fluences (14 or 16 J/cm ²) on the right or left side of the face.	Percentage reductions in mean acne lesion counts from baseline were 42.9% (14 J/cm ²) and 33.9% (16 J/cm ²) after one treatment and 75.1% (14 J/cm ²) and 70.6% (16 J/cm ²) after 3 treatments. There was persistent reduction of 76.1% (14 J/cm ²) and 70.5% (16 J/cm ²) at the 12-month follow-up ($P < .01$). Both objective and subjective improvements in acne scarring and sebum production were noted. Treatment-related pain was well tolerated, and adverse effects were limited to transient erythema and edema at treatment sites.	1B

Photodynamic Therapy	Riddle et al ¹⁵	A non-critical review is presented of a PubMed search for studies examining PDT in the treatment of acne vulgaris.	The authors found 21 clinical trials and case series of various designs. Eight studies employed a split-face design comparing photosensitizer to placebo, no treatment or another photosensitizer. Two trials used three test spots and one control spot per patient. Three studies utilized control subjects receiving no photosensitizer with or without light therapy. All 21 studies reported a reduction in inflammatory lesions and/or a significant improvement in acne. The light sources utilized included blue light, pulsed-dye laser (PDL), intense pulsed light (IPL) and red light. Studies comparing the use of PDT to light therapy alone demonstrated greater improvement in treatment groups pretreated with a photosensitizer.	2A
Orringer et al ¹⁶	To examine the efficacy of PDT using 5-aminolevulinic acid (ALA) and pulsed dye laser therapy in the treatment of acne in a randomized, controlled, split-face, single-blind clinical trial.	Forty-four patients with facial acne were randomized to receive three pulsed dye laser treatments to one side of the face after a 60-90 min ALA application time, while the contralateral side remained untreated and served as a control.	Global acne severity ratings improved bilaterally with the improvement noted to be statistically significantly greater in treated skin than in untreated skin. Erythematous macules (remnants of previously active inflammatory lesions) decreased in number in treated skin when compared with control skin and there was a transient but significant decrease in inflammatory papules in treated skin when compared with untreated skin. There were no other statistically significant differences between treated and untreated sides of the face in terms of counts of any subtype of acne lesion. Thirty percent of patients were deemed responders to this treatment with respect to improvement in their inflammatory lesion counts, while only 7% of patients responded in terms of noninflammatory lesion counts.	1B
Hörfelt et al ¹⁷	To investigate the efficacy and tolerability of MAL-PDT for treatment of moderate inflammatory facial acne in a blinded, prospective, randomized, placebo-controlled multicentre study.	Thirty patients aged 15-28 years with moderate to severe acne were enrolled. Each side of each patient's face was randomly assigned to treatment with MAL (160 mg/g) or placebo cream, applied for 3 h prior to illumination. A second treatment was given 2 weeks later.	A statistically significant greater reduction in the total inflammatory lesion count with MAL-PDT compared with placebo PDT at week 12 was observed; median reduction 54% [95% confidence interval (CI) 35-64%] vs. 20% (95% CI 8-50%), P = 0.0006. MAL-PDT was associated with more pain than placebo PDT, although intensity varied across centers and was reduced with repeated treatment. Local adverse events were consistent with this treatment modality.	1B

(Continued)

TABLE 52-1—Evidence Based Table for Various Non-Medical Interventions in the Treatment of Acne Vulgaris (Continued)

Investigators	Objective	Methods	Results/Conclusions	Level of Evidence
Wiegell and Wulf ¹⁸	To evaluate the efficacy and tolerability of methyl aminolevulinic-based photodynamic therapy (MAL-PDT) in patients with moderate to severe facial acne vulgaris in a randomized, controlled and investigator-blinded trial.	Twenty-one patients were assigned to the treatment group and 15 patients to the control group. The treatment group received two MAL-PDT treatments, 2 weeks apart. Both groups were evaluated 4, 8 and 12 weeks after treatment.	Twelve weeks after treatment the treatment group showed a 68% reduction from baseline in inflammatory lesions vs. no change in the control group ($P=0.0023$). There was no reduction in number of noninflammatory lesions after treatment. All patients experienced moderate to severe pain during treatment and developed severe erythema, pustular eruptions and epithelial exfoliation. Seven patients did not receive the second treatment due to adverse effects.	1B

¹ Ilknur T, Demirtasoglu M, Bicak MU, Ozkan S. Glycolic acid peels versus amino fruit acid peels for acne. *J Cosmet Laser Ther*. 2010 Oct;12(5):242–5.² Kessler E, Flanagan K, Chia C, Rogers C, Glaser DA. Comparison of alpha- and beta-hydroxy acid chemical peels in the treatment of mild to moderately severe facial acne vulgaris. *Dermatol Surg*. 2008 Jan;34(1):45–50; discussion 51. Epub 2007 Dec 5.³ Lloyd JR. The use of microdermabrasion for acne: a pilot study. *Dermatol Surg*. 2001 Apr;27(4):329–31.⁴ Karimipour DJ, Karimipour G, Orringer JS. Microdermabrasion: an evidence-based review. *Plast Reconstr Surg*. 2010 Jan;125(1):372–7.⁵ Baugh WP, Kucaba WD. Nonablative phototherapy for acne vulgaris using the KTP 532 nm laser. *Dermatol Surg*. 2005 Oct;31(10):1290–6.⁶ Leheita TM. Role of the 585-nm pulsed dye laser in the treatment of acne in comparison with other topical therapeutic modalities. *J Cosmet Laser Ther*. 2009 Jun;11(2):18–24.⁷ Karsai S, Schmitt L, Raulin C. The pulsed-dye laser as an adjuvant treatment modality in acne vulgaris: a randomized controlled single-blinded trial. *Br J Dermatol*. 2010 Aug;163(2):395–401. Epub 2010 Apr 15.⁸ Jung JY, Choi YS, Yoon MY, Min SU, Suh DH. Comparison of a pulsed dye laser and a combined 585/1,064-nm laser in the treatment of acne vulgaris. *Dermatol Surg*. 2009 Aug;35(8):1181–7. Epub 2009 Jan 21.⁹ Seaton ED, Charakida A, Mouser PE, Grace I, Clement RM, Chu AC. Pulsed-dye laser treatment for inflammatory acne vulgaris: randomised controlled trial. *Lancet*. 2003 Oct 25;362(9393):1347–52.¹⁰ Orringer JS, Kang S and Hamilton T, Schumacher W, Cho S, Hammerberg C, Fisher GI, Karimipour DJ, Johnson TM, Voorhees JJ. Treatment of acne vulgaris with a pulsed dye laser. A randomized controlled trial, *JAMA* 291 (2004), pp. 2834–2839.¹¹ Papageorgiou P, Katsambas A, Chu A, Br J Dermatol. Phototherapy with blue (415 nm) and red (660 nm) light in the treatment of acne vulgaris. 2000 May;142(5):973–8.¹² Goldberg DJ, Russell BA. Combination blue (415 nm) and red (633 nm) LED phototherapy in the treatment of mild to severe acne vulgaris. *J Cosmet Laser Ther*. 2006 Jun;8(2):71–5.¹³ Na JI, Suh DH. Red light phototherapy alone is effective for acne vulgaris randomized, single-blinded clinical trial. *Dermatol Surg*. 2007 Oct;33(10):1228–33; discussion 1233.¹⁴ Jih MH, Friedman PM, Goldberg LH, Robles M, Glaich AS, Kimyai-Asadi A. The 1450-nm diode laser for facial inflammatory acne vulgaris: dose-response and 12-month follow-up study. *J Am Acad Dermatol*. 2006 Jul;55(1):80–7.¹⁵ Riddle CC, Terrell SN, Menser MB, Aires DJ, Schweiger ES. A review of photodynamic therapy (PDT) for the treatment of acne vulgaris. *J Drugs Dermatol*. 2009 Nov;8(11):1010–9. Review.¹⁶ Orringer JS, Sachs DL, Bailey E, Kang S, Hamilton T, Voorhees JJ. Photodynamic therapy for acne vulgaris: a randomized, controlled, split-face clinical trial of topical aminolevulinic acid and pulsed dye laser therapy. *J Cosmet Dermatol*. 2010 Mar;9(1):28–34.¹⁷ Hörfelt C, Funk J, Frohm-Nilsson M, Wiegleb Edström D, Wennerberg AM. Topical methyl aminolevulinate photodynamic therapy for treatment of facial acne vulgaris: results of a randomized, controlled study. *Br J Dermatol*. 2006 Sep;155(3):608–13.¹⁸ Wiegell SR, Wulf HC. Photodynamic therapy of acne vulgaris using methyl aminolevulinate: a blinded, randomized, controlled trial. *Br J Dermatol*. 2006 May;154(5):969–76.

TABLE 52-2— Strength of Recommendation for the Use of Following Modalities in the Treatment of Acne

Chemical peels	B
Microdermabrasion	B
532 nm KTP laser	B
585 nm pulsed dye laser	B
Visible light (red light/bluee light/mixed red and blue light)	B
1450 nm diode laser	B
Photodynamic therapy	A (consistent results seen in high quality studies)

the areas applied. In addition, salicylic acid is a volatile compound and leaves no active agent after 4 minutes of topical application.⁴⁰ Unlike glycolic acid, the patient does not require buffering and the topical application can be visually quantified by the doctor based upon the amount of the white precipitate to achieve the desired effect.

There have been many studies evaluating the efficacy of these peels in different populations and skin types^{41–44}. In addition, studies have been conducted to compare glycolic and salicylic acid peels, but such studies are few in number. A recent, split-faced, double-blind trial compared a 30% concentration of each compound on 20 individuals every other week for 3 months.⁴⁵ There was a decrease of acne lesions in the salicylic acid group, which persisted 2 months after the last peel, whereas patients in the glycolic acid group displayed new acne lesions after discontinuation of peeling. However, this difference in lesion counts was small and not statistically significant, and patients did not seem to favor salicylic acid over glycolic acid.

Application of sunscreen and strict protection from the sun is essential with any chemical peel and should be explained to the patients very clearly.

CONCLUSION

Both glycolic and salicylic acid peels appear to be effective in achieving superficial epidermolysis, which leads to an improvement in a variety of different forms of acne as seen in the treatment of a number of different patient populations and skin types.

Microdermabrasion

How is microdermabrasion helpful in management of acne?

Microdermabrasion involves propelling polyester or nylon bristles or an element (e.g., aluminum oxide crystals) onto the face at various speeds, then vacuuming off the

TABLE 52-3— The Levels of Evidence are as Outlined by Sackett and Colleagues in *Evidence-Based Medicine: How to Practice and Teach EBM*

1A	Systematic review of randomized controlled trials
1B	Randomized-controlled trial with narrow confidence interval
1C	All or none case series
2A	Systematic review of cohort studies
2B	Cohort study/low quality randomized-controlled trial
2C	Outcomes research
3A	Systematic review of case-controlled studies
3B	Case-controlled study
4	Case series, poor cohort case controlled
5	Expert opinion

Strength of Recommendation reference

A—Recommendation based on consistent and good-quality patient-oriented evidence.

B—Recommendation based on inconsistent and limited-quality patient-oriented evidence.

C—Recommendation based on consensus, usual practice, opinion, disease-oriented evidence, or case series for studies of diagnosis, prevention, treatment and screening.

debris using a specialized wand or handpiece. The vacuum suction can be operated at various pressures, allowing the operator to control both particle speed and suction at the skin surface. Common complications include eye irritation, which ranges from chemosis and tearing to photophobia to punctate keratitis if crystals adhere to the corneal epithelium.⁴⁶ Microdermabrasion was originally shown to be beneficial in patients in acne.^{47–49} More recently, microdermabrasion has been combined as a pretreatment with aminolevulinic acid (ALA) photodynamic therapy (PDT) or chemical peels to get better results.⁵⁰ Removing the superficial stratum corneum allows greater penetration of ALA, and PDT seems to have greater improvement in comedonal and even inflammatory acne lesions. Wang et al. compared the efficacy, safety, and pain associated with the treatment of inflammatory facial acne with the 1,450 nm laser alone versus microdermabrasion plus the 1,450 nm laser, in a randomized split face trial. Although laser alone and microdermabrasion plus laser significantly reduced the total number of acne lesions, this small pilot study with 20 patients did not demonstrate increased clinical efficacy or decreased associated pain with the addition of microdermabrasion to treatment with the 1,450 nm laser.

CONCLUSION

Microdermabrasion can be used as an adjuvant for enhancement of efficacy of PDT for treatment of acne scars.

Lasers and Light Devices

How do laser and light devices help in management of acne?

The increase of bacterial resistance and the adverse effects and lack of response to usual therapies has led to the investigation of new therapeutic alternatives such as the laser and light-based devices. The main potential targets for light sources are the infundibulum, the sebaceous glands, *P. acnes* and the inflammatory response. The laser and light devices can help reduce/clear acne broadly by either or both of the two mechanisms of action:

- The shorter wavelengths such as the 532 nm, 585 nm and 595 nm pulsed dye laser (PDL) are absorbed by the porphyrins contained in the *P. acnes* and cause thermal damage leading to bacterial destruction.⁵¹ Different studies have shown results in favor of and against this theory, with various degrees of clearance achieved with their use in treating acne.
- The longer wavelength lasers such as 1450 nm diode laser and photodynamic therapy focus on decreasing the size of sebaceous glands by their deeper penetration into the skin. The shrunken sebaceous glands result in decreased sebum production and improvement of acne.

532 nm Potassium titanyl phosphate (KTP) laser

The optical penetrance of green light at 500-532 nm has been shown to be greater than that of blue light in studies probably because of its innate characteristic of activating bacterial porphyrins.⁵² In a study with 175 patients with mild to severe acne, three groups of patients were used to compare three treatments for acne: first group received laser treatment with 532 nm alone, second group received laser treatment with topical and cleansing agents used after completing 6 sessions of laser treatments and third group was treated with topical and cleansing agents concurrently with laser therapy.⁵³ Six weekly laser sessions were used with 30- to 40-millisecond pulse duration and 6 to 12 J/cm² of energy with continuous contact cooling. Although decrease in lesion counts and clearance rates of 60-70% were achieved in first group, 90% of patients in the third group demonstrated 80-95% improvements in their inflammatory lesions. Of the third group, more than 50% of the patients were able to maintain their outcomes for up to 4 months without any further treatments.

In another later study with 26 patients with moderate to severe acne, the safety and efficacy of 532 nm KTP laser for treatment of acne was studied.⁵⁴ In this split face study, one side of the face for each patient served as the treatment half and the other side as a control. Four laser exposures with 532 nm laser were given to these patients and results

were assessed at 1 and 4 weeks postfinal treatment. A mean score of 34.9% and 20.7% reduction was noted at 1- and 4-week respectively, calculated using Michaësson acne severity score. No side effects occurred. These findings indicated that KTP 532 nm laser is safe and effective for treating acne.

585 nm Pulsed Dye laser (PDL)

The PDL emits a beam of visible coherent light and targets oxyhemoglobin in microvessels. Traditionally used to treat vascular lesions of the skin, PDL can cause significant discomfort and purpura that is generally transient, but may persist for long in certain cases. In addition, it carries a higher risk of hyperpigmentation especially in patients with darker skin types, requiring extra caution. PDL can target inflammatory component of acne by using hemoglobin as the chromophore. Moreover, it seems to induce release of antiinflammatory molecules by stimulating T-cells.⁵⁵ Use of low fluence induces production of procollagen secondary to heating of the perivascular dermis, a process that may help reduce acne scarring, comedo formation, and maturation of follicular wall.^{56,57} PDL has been studied for treating scars and shown to be very efficacious.^{58,59} In a recent study, treatment of acne in comparison with other topical therapeutic modalities was evaluated in 45 patients with mild to moderate acne.⁶⁰ Patients were randomly divided into three groups: group A received treatment with pulsed dye laser therapy every 2 weeks, group B received topical preparations and group C was subjected to chemical peeling using trichloroacetic acid 25%. At 12 weeks of treatment, there was a significant improvement of the lesions within each group with the best results seen in group A; however, no significant difference was detected between the three treatment protocols after the treatment period. Remission in the follow-up period was significantly higher in the first group.

Seaton et al. compared the efficacy and tolerability of PDL treatment in 41 adults with mild-to-moderate facial inflammatory acne in a double-blind, randomized-controlled trial 41 adults with were enrolled.⁶¹ Patients were randomly assigned to PDL or sham treatment. Treatment was given at baseline and patients were seen after 2, 4, 8, and 12 weeks. After 12 weeks, acne severity was reduced from 3.8 to 1.9 in the PDL group and 3.6 to 3.5 in the sham group ($p=0.007$). Treatment was well tolerated. Total lesion counts fell by 53% in PDL patients and 9% in controls ($p=0.023$), and inflammatory lesion counts reduced by 49% in PDL patients and 10% in controls ($p=0.024$). The most rapid improvements were seen in the first 4 weeks after treatment. This suggests that PDL therapy improves inflammatory facial acne 12 weeks after one treatment with no serious adverse effects.

On the other hand, Orringer and colleagues conducted a split face, single-blind, randomized-controlled trial to

assess the efficacy of 585 nm PDL with 350- μ s pulse duration, 7 mm spot size and 3-J/cm² energy.⁵¹ The treated halves had significant reduction in papules from baseline to week 12, but the untreated sides also showed reduction, thus resulting in an overall statistically insignificant difference. In addition, despite the consideration of the large dropout rates from the study, the authors concluded that PDL was not very efficacious in treating acne.

595 nm Pulsed Dye Laser

In a study by Yoon et al. 595 nm PDL was shown to be useful for reducing acne associated erythema in 20 patients using two successive sessions with a 595-nm PDL at 4-week intervals.⁶² A total of 90% of acne erythema patients achieved clinical improvement. Lesion counts decreased 24.9% after the first treatment ($p<0.05$) and by 57.6% (versus baseline) after the second treatment ($p<0.05$). Significant improvements were also noted in mean Leeds scores, erythema indexes, and skin elasticities after each treatment. Treatment-related pain was well-tolerated and adverse effects were limited to transient erythema and edema at treatment sites.

The 595-nm pulsed dye laser (VBeam; Candela Corp.) has also been used in conjunction with the 1450-nm diode laser (Smoothbeam; Candela Corp., Wayland, MA) to treat both acne vulgaris and postinflammatory erythema resulting from acne. Glaich et al. in a noncontrolled study of 15 patients, demonstrated that the lesions counts dropped by a mean of 52%, 63%, and 84% after 1, 2, and 3 treatments, respectively ($p<0.01$).⁶³ In addition to improvements in acne and acne scarring, significant improvement in postinflammatory erythema was also noted and may be attributed to the selective photothermolysis of vessels by the pulsed dye laser.

UV radiation

Although no controlled studies have been conducted, UVB resulted in nontherapeutic minor effects.⁶⁴ Short-term improvement may be seen, probably because of the anti-inflammatory effects of UV radiation. However, UV radiation generates squalene peroxide from the sebum lipid, squalene, which in animal models has been shown to be comedogenic.^{65,66} In addition, UV radiation's carcinogenic abilities cannot be ignored.

Visible light

Na and Su assessed the efficacy of red light phototherapy with a portable device in acne vulgaris in a split-face randomized-controlled single-blinded trial on 28 volunteers with mild-to-moderate acne.⁶⁷ The right or left side of the face was randomized to treatment side and phototherapy was performed for 15 minutes twice a day

for 8 weeks. The percent improvement in noninflammatory and inflammatory lesion counts of the treated side was significant compared to the control side ($p<.005$). Visual Analog Scale decreased from 3.9 to 1.9 on the treatment side and the difference between the treatment and control sides was significant at week 8 ($p<.005$), suggesting that red light has the potential for being used as a single treatment for acne.

De Arruda et al. evaluated the efficacy and safety of blue light treatment versus topical benzoyl peroxide 5% formulation in patients with acne grades II and III by enrolling 60 volunteers with facial acne.⁶⁸ Thirty of them were irradiated with blue light (8 times, twice a week) and the other thirty were treated with topical benzoyl peroxide 5% formulation, auto-applied twice a day, every day. The improvement achieved by the blue light was the same as the one with benzoyl peroxide, regardless of the type of lesion ($p=0.05$). The side effects were less frequent in the group treated with blue light. Gold et al. in a multicenter clinical evaluation evaluated the safety and efficacy of a new blue light source in the treatment of mild to moderate inflammatory acne vulgaris in comparison to topical 1% clindamycin solution.⁶⁹ Blue light therapy reduced inflammatory acne vulgaris lesions by an average of 34%, compared to 14% for topical 1% clindamycin solution.

In a study, blue light (peak at 415 nm) and a mixed blue and red light (peaks at 415 and 660 nm) were evaluated in the treatment of acne vulgaris.⁷⁰ One hundred and seven patients with mild to moderate acne vulgaris were randomized into four treatment groups: blue light, mixed blue, and red light, cool white light and 5% benzoyl peroxide cream. After 12 weeks of active treatment, a mean improvement of 76% (95% confidence interval [CI] of 66-87%) in inflammatory lesions was achieved by the combined blue-red light phototherapy which was significantly superior to that achieved by blue light (at weeks 4 and 8 but not week 12), benzoyl peroxide (at weeks 8 and 12) or white light (at each assessment). The final mean improvement in comedones by using blue-red light was 58% (95% CI of 45-71%), again better than that achieved by the other active treatments used, although the differences did not reach significant levels. This study suggested that phototherapy with mixed blue-red light, probably by combining antibacterial and anti-inflammatory action, is an effective means of treating acne vulgaris of mild to moderate severity with no significant short-term adverse effects.

Another study alternated blue and red light treatments in 24 subjects with Fitzpatrick skin types II-V and mild to severe symmetric facial acne vulgaris. They used eight sessions, two per week 3 days apart alternating between 415 nm blue light (20 minutes/session, 48 J/cm²) and 633 nm red light (20 minutes/session, 96 J/cm²) from a light-emitting diode (LED)-based therapy system.⁷¹ Of the twenty-two patients who completed the trial, the mean lesion count reduction was significant at 46% ($p=0.001$). At the 12-week follow-up, the mean lesion count reduction was

also significant at 81% ($p=0.001$). Severe acne responded best, while inflammatory lesions responded better than comedones. Besides, the treatments were free of pain and other side effects.

1450 nm diode lasers

The 1450 nm laser with dynamic cooling device is FDA-approved for the treatment of acne. The 1450 nm laser targets the water in the upper dermis, remodels the underlying collagen and improves facial and periorbital rhytides. The improvement in acne lesions was noticed when some patients received facial rejuvenation with this laser⁷² and is possibly caused by thermal damage caused to the sebaceous glands arresting their sebaceous output in a temporary manner.⁷³

Paithankar et al. used four sessions of 1450 nm laser 3 weeks apart on 27 patients and showed a significant clearance of inflammatory acne that lasted 6 months. Erythema was reported as the most common side-effect and hyperpigmentation was experienced in 3 patients.⁷⁴ Jih et al. evaluated the dose response of a 1450-nm diode laser for treatment of facial acne, sebum production, and acne scarring utilizing two laser fluences and to determine long-term remission after laser treatment.⁷⁵ Twenty patients (Fitzpatrick skin phototypes II-VI) received 3 treatments using the 1450 nm diode laser (3-4 week intervals). Split face comparisons were performed by randomizing patients to one of two fluences (14 or 16 J/cm²) on the right or left side of the face. Percentage reductions in mean acne lesion counts from baseline were 42.9% (14 J/cm²) and 33.9% (16 J/cm²) after one treatment and 75.1% (14 J/cm²) and 70.6% (16 J/cm²) after 3 treatments. There was persistent reduction of 76.1% (14 J/cm²) and 70.5% (16 J/cm²) at the 12-month follow-up ($P < .01$). Both objective and subjective improvements in acne scarring and sebum production were noted. Treatment-related pain was well tolerated, and adverse effects were limited to transient erythema and edema at treatment sites.

Although 1450 nm diode laser has been shown to be effective in treating acne, the pain associated with the treatment is a limiting factor. For the same efficacy, higher fluences with single pass have been demonstrated to be associated with more pain as compared to a double pass lower fluence protocol.⁷⁶ However, this doubled the treatment times. A new laser which possesses a spot size four-fold larger than the previous lasers reduced the treatment times more than fourfold. Bernstein studied this new laser and demonstrated that the Allen Smith acne scores decreased from 2.7 pre-treatment to 2.0 post-treatment and lesion counts decreased from an average of 34.4 pre-treatment to 16.1, 2 months post-treatment.⁷⁷ Pain ratings on a 1 to 10 scale averaged 4.9. All subjects rated their skin as less oily at the follow-up period.

In another recent study, Laubach et al. aimed to study the mechanism of action of the 1450 nm diode laser in acne

reduction and its effects on sebum excretion rate (SER).⁷⁸ No significant reduction in SER was observed on all treatment sites ($P > 0.05$) on the nose. Reduction in the absolute SER was observed for both test and control sites on the forehead, reaching significance on the treatment site ($P = 0.04$) and marginal significance on the control site ($P = 0.08$).

1540 nm Er:glass laser

In a study with 2-year follow-up, Angel et al. evaluated the efficacy of 1540 nm Er:glass laser with four treatments at 4-week intervals in 25 patients with acne severity greater than 3 on the Burton scale. In this group, the mean percent reduction was 71%, 79%, and 73% at 6-month, 1-year and 2-year follow-up respectively.⁷⁹ No side effects were reported. All patients commented that their skin was less prone to oiliness. Biopsies taken after treatment showed progressive rarefaction and miniaturization of sebaceous glands and pilosebaceous follicles without morphologic damage to epidermal and dermal structures.

Kassir et al. performed another study on the 1540 nm Er:glass laser with an active cooling contact device for 4 treatment sessions at 2 weeks intervals on 20 patients with inflammatory acne and observed a lesion count reduction of 70% with follow-up evaluations at 1 and 3 months without any side-effects.⁸⁰

Randomized-control trials (RCTs) are required to assess the role of 1,540 nm Er:glass laser in acne and provide a higher level of evidence.

Photopneumatic technology

Photopneumatic technology (Isolaz™, Aesthera Inc., Pleasanton, CA) combines vacuum pressure with a broadband light source device has been designed to attack multiple targets for the effective treatment of acne. The vacuum draws the target tissue into the treatment tip of the device, raising the sebaceous glands and opening the pores to empty the trapped sebum and necrotic cell. This decreases the proliferation of *P. acnes*.

Gold and Biron demonstrated reduction in inflammatory lesion counts for at least 3 months after the final treatment in 11 subjects.⁸¹ They received 4 treatments at 3 week intervals and were seen after at 1 and 3 months. At 3 months, reductions in lesion counts were significant for inflammatory ($P = .0137$) and noninflammatory ($P = .0383$) lesions. Mean scores between visits consistently dropped sharply from their immediate post-treatment values for pain, erythema, and edema. Nine out of the eleven subjects were moderately satisfied to very satisfied with treatment.

Another study with 20 patients with mild to severe acne was performed to determine the clinical efficacy and side-effect profile of photopneumatic therapy for the treatment of facial acne vulgaris. These patients received four successive treatments at 2-week intervals with a

combined photopneumatic device.⁸² Modest reduction in acne lesion counts and global clinical improvement was seen in the majority of patients. Best clinical improvement was noted in patients with severe acne. Side effects were mild and limited to transient erythema and rare purpura. Most patients experienced worsening of acne early in the treatment course.

As this is a relatively new modality being explored, good quality RCTs are still awaited to provide better evidence of the usefulness of photopneumatic technology in acne therapy.

Intense pulsed light (IPL)

Intense pulsed light or flash lamps are high energy light sources that emit a broad spectrum of wavelengths in the visible and near-infrared spectrum. IPL has been used in photodynamic therapy for acne as the light source, but IPL alone for treating acne has not been studied enough. In a split face study with 30 female patients with mild-moderate acne, benzoyl peroxide (BP) gel was applied to one side of the face and also treated with the PR filter (acne filter) of the IPL.⁸³ On the other side, only benzoyl peroxide was used. Although all patients experienced the reduction of inflammatory lesion counts in both sides of face, there was no significant difference between IPL-treated and untreated sides of the face for mean papule plus pustule counts 3 weeks after three sessions. Reduction in redness was better observed on the side that was treated with the IPL.

In another study involving IPL, 3 treatments were compared. Adapalene alone, IPL combined with adapalene and PDT with methyl aminolevulinic acid (MAL), and IPL plus adapalene.⁸⁴ There were no significant differences in the treatment results with any of the 3 treatments.

Recently, IPL was compared with PDL concerning efficacy and safety, in a study by Choi et al. with 20 patients with facial acne. Treatment was performed 4 times at 2-week intervals.⁸⁵ Numbers of total acne lesions decreased following both treatments. For inflammatory lesions such as papules, pustules and nodules, IPL-treated sides showed an earlier and more profound improvement than PDL-treated sides. However, at 8 weeks after the 4th treatment, a rebound aggravation of acne was observed on IPL-treated sides. On the contrary, PDL produced gradual improvements during the treatment sessions and these improvements lasted 8 weeks after the 4th treatment. Noninflammatory lesions as open and closed comedones also showed improvement following both treatments and PDL-treated sides showed better improvement as the study proceeded. Histopathologic examinations showed amelioration in inflammatory reactions and an increase in TGF-beta expression after both treatments, which were more prominent for PDL-treated sides.

The paucity of studies with IPL for use in treating acne makes it an uncertain option for acne management.

Photodynamic therapy (PDT)

Photodynamic therapy works on the principle of a multistep process which involves uptake of a photosensitizer agent by target cells more than healthy cells followed by exposure of this part of the body to light source. This activates the photosensitizer leading to repairable (local changes to redox state of cell) and irreparable (cell death) changes to cells. The main toxic agents produced in this process are singlet oxygen or reactive oxygen species that oxidize biologic molecules. The oxidative stress induces stress proteins such as heat shock and glucose-regulated proteins.^{86,87}

P. acnes produces endogenous porphyrins, predominantly coproporphyrin III. This absorbs mainly visible light in the range of 400 to 415 nm.^{88,89} The emission maximum for coproporphyrin is at 623 nm.⁸⁹ Studies have shown that irradiation of the affected acne skin with UV (390 nm), violet (405 nm), blue (415 nm), green (470 nm), white (full spectrum) and red (660 nm) improves the state of the skin to varying degrees depending on the wavelength and the dose of the light.⁹⁰⁻⁹¹ Though the blue and the violet wavelengths have the most effective activation of *P. acnes* porphyrin, they have poor penetration depth in the skin.^{90,91,70} In this regard, the green light is also a good choice, but the red light has deeper penetration into the tissues even if it is less effective in activating porphyrins. Red light has wound healing properties as well, since it induces the release of proinflammatory cytokines from macrophages, which in turn stimulate fibroblast proliferation and growth factor production.^{92,93}

The photodynamic killing of bacteria can be enhanced by modification of sebaceous gland apparatus with exogenous inductive agents such as aminolevulinic acid (ALA) which is the photosensitizer. Photodynamic therapy with 5-aminolevulinic acid and recently methyl aminolevulinate (MAL) has been shown to be a safe and effective modality for the treatment of acne vulgaris.⁹⁴ Consensus guidelines suggest that 30 to 60 minutes is sufficient 5-aminolevulinic acid contact time before photoactivation with blue light, red light, yellow light, broadband light, halogen, or pulsed dye laser devices. An average of three treatments can yield significant long-term improvement. Photosensitizers activated by visible and near-infrared (NIR) laser irradiation, which have deep penetration within the tissue, are preferred.

In a recent study, the effect of PDT with ALA and red light (550-700 nm) was studied on comedo formation using the Cyanoacrylate follicular biopsy (CFB), a noninvasive procedure proposed as the most reliable modality of studying follicular casts.⁹⁵ In 10 patients with mild-to-moderate facial and/or chest/back acne resistant to conventional therapies, ALA PDT at 2-week intervals in 3 sessions was given. Four weeks after their last PDT session, the patients showed an average global score reduction of 50%. CFBs demonstrated a reduction in the total area, the average area and the density of macrocomedones suggesting that ALA-PDT does exert an action on the comedogenic phase of acne.

In another study, PDT with an intralesional injection of ALA (ILI-PDT) was studied for its efficacy and safety in patients with recalcitrant localized acne.⁹⁶ In 10 patients of Fitzpatrick III and IV, ILI-PDT showed a statistical superiority in effect after the first and second PDT compared to conventional PDT. In addition, ILI-PDT can reduce the total number of PDT sessions and can cut down the overall cost. Generalized erythema and exfoliation were not reported after ILI-PDT. Focal treatment in the ILI group may account for such findings, but as most PDT side effects are associated with the epidermal damage, it is natural to expect less irritation with an ILI method in which ALA is delivered directly to the dermis.

ALA is a hydrophilic molecule and thus has limited penetration through cellular membranes and into the interstitial space of tissues. Methyl aminolevulinate (MAL) is an ester of ALA with enhanced lipophilicity. MAL is de-esterified into ALA by intracellular enzymes. MAL should be expected to penetrate more easily and deeper into the targeted lesion⁹⁷ and studies have demonstrated that MAL is more selective towards abnormal skin than ALA.⁹⁸

Wiegell and Wulf compared the treatment effects and tolerability of ALA-PDT versus MAL-PDT in the treatment of acne vulgaris in a controlled randomized investigator-blinded trial on 15 patients.⁹⁹ There was a 59% decrease in inflammatory lesions at 12 weeks after treatment with no significant differences in effectiveness between the two treatments. All patients experienced moderate to severe pain during illumination and developed erythema, pustular eruptions, and epithelial exfoliation after treatment, which were more severe and uniform in the ALA-PDT-treated area.

Twenty percent ALA may have phototoxic side effects which can limit its use. The 5-ALA concentration can be lowered by a factor of 40 by changing the vehicle of 5-ALA from a moisturizing cream to liposome encapsulation. de Leeuw et al. assessed the efficacy and the safety of PDT using 5-ALA 0.5% in liposomal spray and intense pulsed light (IPL) in combination with topical peeling agents (Li-PDT-PC) in acne vulgaris.¹⁰⁰ After a mean of 7.8 months and 5.7 treatments, the mean total number of lesions reduced from 34.6 lesions to 11.0 lesions, resulting in a mean improvement of 68.2%. Side effects were minimal.

Indocyanine green (ICG), often used as a diagnostic dye, has its maximum absorption between 650 and 800 nm.¹⁰¹ It has been used a photosensitizer, and combined with diode laser irradiation has been applied for acne treatment. This is based on the principle of selective photothermolysis of sebaceous glands.

Studies have shown that multiple treatments with a combination of ICG and NIR irradiation reduced inflammation and improved the state of the skin for a month without any side effects.¹⁰² In a study with 22 patients with facial or back acne, ICG application and NIR laser-diode light (803 or 809 nm) irradiation were performed.¹⁰³ One mg/mL solution of ICG was applied for 5 or 15 minutes to the cleaned skin site. Untreated, only stained, and only

light irradiated skin areas served as controls. For soft acne treatment, the low-intensity (803 nm, 10-50 mW/cm², 5-10 minutes) or the medium-intensity (809 nm, 150-190 mW/cm², 15 minutes) protocols were used. The observations during 1-2 months showed that soft acne treatment decreased the number of active elements, reduced erythema and inflammation, and considerably improved the skin state without side effects. At high power densities (up to 200 W/cm²), ICG-stained acne inflammatory elements were destroyed for light exposures of 0.5 seconds.

Different incubation times may yield variable outcomes. This idea was studied recently where incubation times of 30 minutes and 3 hours were compared in PDT with intense pulsed light for inflammatory acne.¹⁰⁴ The 20 Korean patients enrolled in the study were randomized into 2 groups: short incubation with ALA plus IPL (30 minutes) or long incubation with ALA plus IPL (3 hours) on one side of face and IPL alone on the other side of the face for 3 monthly sessions. All the patients showed significant improvement after 3 treatments, but the degree of improvement was highest in the group with ALA-PDT plus 3 hour incubation. All groups showed reduction in sebum secretion after the 3 sessions but the differences among the groups did not show significance. Mild side effects such as transient erythema and mild edema were reported.

Radiofrequency

Radiofrequency (RF) has been used for nonablative skin rejuvenation and is believed to work on the principle of heat-induced skin remodeling and tightening.^{105,106} There have been three types of radiofrequency devices in use: monopolar, bipolar, and tripolar. Unfortunately, the role of radiofrequency in management of acne has not been studied well and not defined, except that it has been shown to lower sebum secretion.¹⁰⁷ A study was conducted in which IPL, combination of RF and IPL, and blue light in photodynamic therapy were studied for acne vulgaris. Twenty-two patients with moderate to severe acne vulgaris were randomly assigned to receive ALA-PDT with photoactivation by intense pulsed light (IPL, 600-850 nm), a combination of IPL (580-980 nm) and bipolar radiofrequency (RF) energies, or blue light (417 nm).¹⁰⁸ Each patient received 3 ALA-PDT sessions at 2-week intervals. At 1 month and 3 months, median lesion count reduction percentages were highest with IPL activation and lowest with blue light activation, although the differences did not reach statistical significance. ALA-PDT with activation by IPL appears to provide greater, longer-lasting, and more consistent improvement than either RF-IPL or blue light activation in the treatment of moderate to severe acne vulgaris.

A series of 4 case reports were published by Braun who used the combination of radiofrequency and blue light for acne treatment.¹⁰⁹ He suggested that this combination provided a method of treating acne that was rapid, caused no downtime, pain, erythema, peeling; safe in all

skin types, caused skin tightening and not associated with bacterial resistance. This combination could be used as an option for treating cystic acne but more data and research needs to be available for considering them more effective. Observational studies using a combination of IPL (400 to 980 nm) and radiofrequency have shown improvement in patients with moderate acne, but the effect of RF is not clear, as IPL being an effective treatment by itself may have overshadowed it.^{110,111}

Larger studies with good design can aid in placing Radiofrequency in the treatment spectrum of acne.

CONCLUSION

Evidence suggests that shorter wavelengths such as 532 nm, 585 nm and 595 nm PDL are absorbed by the porphyrins in *P. acnes* and cause thermal damage leading to bacterial destruction. The longer wavelength lasers such as 1450 nm diode laser and PDT focus on decreasing the size of sebaceous glands by their deeper penetration into the skin. Radiofrequency may have a role in reducing sebum secretion and thus help reduce acne.

Botox

Does Botox have a role in management of acne?

Botulinum toxin A (BTX-A) or BOTOX® is currently FDA-approved for the treatment of blepharospasm and strabismus associated with dystonias (including benign

essential blepharospasm or cranial nerve VII disorders) in patients aged 12 years or older and for the treatment of cervical dystonia in adults. Myobloc (botulinum toxin type B) is currently FDA-approved for the treatment of cervical dystonia. However, the most prevalent and popular use of Botox is for cosmetic purposes and is an off-label use.¹¹²

The property of botulinum toxin that led to the idea of its role in acne treatment is the different pathways that may be utilized by BTX-A in inhibiting formation of acne. These are mainly 3 pathways:

- BTX inhibits sebum production by sebaceous glands through cholinergic inhibition. Botulinum toxins block acetylcholine release, causing a chemical denervation. Neurotransmission at the neuromuscular junction involves the release of acetylcholine from the presynaptic nerve terminal. Acetylcholine (Ach) release requires docking and binding of the neurotransmitter vesicles to the presynaptic membrane. This is also the mechanism by which it acts a muscle relaxant and helps improve wrinkles and facial lines. Decreased sebum production reduces the growth of *P. acnes*.
- BTX also inhibits sweat production from the sweat glands. Reduction in perspiration improves acne by decreasing the *P. acnes* growth.¹¹³ This may help in acne reduction.
- Keratinocytes occlude the follicles and play a role in causing acne. Migration of keratinocytes is inhibited by high-dose stimulation of nicotinic ACh receptors and by inhibiting the release of Ach, BTX can indirectly increase the migration of keratinocytes and reduce follicular occlusion.¹¹⁴

What We Know

- Acne is a disease of pilosebaceous unit with multifactorial etiology characterized by comedones, papules, pustules, nodules and cysts- inflammatory and/or noninflammatory lesions, which commonly result in scarring.
- 60-70% of the population of USA is affected by acne at some time in their lives.
- Acne has multifactorial etiology with four major factors: follicular hyperproliferation, subsequent follicular plugging, excess sebum production, and the activity of *P. acnes* causing inflammatory response of the tissue.
- The newer etiologic factors demonstrated to be contributory in acne development include a genetic component, retention hyperkeratosis, hormones (androgens, IGF etc.), inflammatory activity of *P. acnes* via toll-like receptors, *P. acnes* lipase activity, diet (western diets and chocolate).
- Increase of bacterial resistance has led to investigation of new therapeutic options.
- Chemical peels constitute a nonlaser therapeutic option for superficial exfoliation and aid in hastening the process of resolution of comedones by their transition to superficial epidermis.
- Shorter wavelengths such as 532 nm, 585 nm, and 595 nm pulsed dye laser are absorbed by the porphyrins in *P. acnes* and cause thermal damage leading to bacterial destruction.
- The longer wavelength lasers such as 1450 nm diode laser and photodynamic therapy focus on decreasing the size of sebaceous glands by their deeper penetration into the skin.
- Radiofrequency has been shown to reduce sebum secretion and thus help reduce acne.
- Botox is a new modality for acne. It works by inhibiting sebum production of sebaceous glands through cholinergic inhibition, inhibits sweat production, thereby decreasing growth of *P. acnes* and also by indirectly increasing the migration of keratinocytes which may reduce follicular occlusion.
- *P. acnes* vaccine that consists of cell-wall anchored sialidase of *P. acnes* has shown in-vivo protective immunity in animal models.

It is still in its very early stages to comment and conclude about the use of BTX in acne therapy, although a potential role can be foreseen.

Future Directions

P. acnes vaccines

P. acnes vaccine is an interesting concept and has been developed for *P. acnes*-associated inflammatory acne. It consists of a cell-wall anchored sialidase of *P. acnes* or killed whole organism of *P. acnes*. Intranasal immunization of mice with this vaccine provided in-vivo protective immunity against *P. acnes* challenge. In addition, it decreased the *P. acnes*-induced elevation of cytokine production.¹¹⁵ The antibodies elicited by inactivated *P. acnes* attenuated IL-8 production in human sebocytes but no effect was seen on *P. acnes* growth.¹¹⁶ Besides, there was reduced ear swelling and decreased release of proinflammatory macrophage inflammatory protein (MIP-2) cytokine. This study in the murine model suggests that antibodies against *P. acnes* that exhibit antiinflammatory properties yield clinical improvement, though they may lack antimicrobial effect.

CONCLUSIONS

Medical treatments of acne – traditional and new therapies are great modalities for acne management, but with the development of bacterial resistance to these drugs, alternative treatments are being explored. Some of these have proven to be better than the existing therapies while others are still under research and show potential as treatments for acne. In addition, some of these newer modalities have demonstrated great results when used in combination with topical medications. With experience and a thorough understanding of all the available nonmedical interventions, the doctor and patient can decide upon the best course of action for treating acne.

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Sick Building Syndrome: Cutaneous Manifestations

53

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INTRODUCTION

During the past 40 years, health problems related to indoor air quality (IAQ) have received increasing attention. “Sick” buildings were reported in the 1950s but have become a recognized occupational health problem since the 1970s.^{1,2} In 1982, a World Health Organization (WHO) expert group produced a definition of “Sick building syndrome” (SBS).¹ This definition, based mainly on reports from the Scandinavian countries and the United States, is still in widespread use and includes a list of general, mucosal, and skin symptoms and signs (Table 53-1).

This definition, however, does not relate to an accepted clinical syndrome but is rather a list of symptoms often experienced by individuals working or residing in buildings with indoor climate problems. Consequently, the concept of SBS has been given a different meaning by various investigators; for example, Anglo-American investigators often exclude skin symptoms.³ Criteria for the definition of SBS have been suggested. These include specific symptoms and signs plus odor or taste sensations reported by a threshold number of occupants of the building. The cause must not be exposure to a single agent.⁴ These criteria, however have never been validated.

The term “sick building syndrome” has been widely criticized,^{5,6} mainly because it implies a cause or attribution of the symptoms. SBS is commonly separated from “building related illnesses” (BRI), which comprises established illnesses where the indoor environment factor causing the symptoms is often well known, such as hypersensitivity pneumonitis, humidifier fever and Legionnaire’s disease.³ Another suggested terminology, which has come into use

gradually is “specific building-related illnesses” as opposed to “nonspecific building-related illnesses” which includes SBS.⁷

The cause of or rather risk factors for SBS have been reviewed^{8–11} and the syndrome is generally described as having a multifactor background. Consistent risk factors reported are the female gender, atopy, psychosocial stress, low outdoor airflow rate, and indoor chemical exposure.^{8–11}

There are other environmental syndromes described that are closely connected to SBS. Carbonless copy paper (CCP) has been used since the 1940s, extensively so during the 1970s to 1990s. Skin, mucosal, and general symptoms have been reported when CCP is handled intensively and especially in small, badly ventilated areas.^{12–13} Reports of symptoms related to CCP are currently very sparse.

Since the 1980s, a phenomenon known as multiple chemical sensitivities (MCS) has attracted great interest and there are numerous related publications. Cullen¹⁴ has defined MCS as “an acquired disorder characterized by recurrent symptoms, referable to multiple organ systems, occurring in response to demonstrable exposure to many chemically unrelated compounds at doses far below those established in the general population to cause harmful effects. No single widely accepted test of physiologic function can be shown to correlate with symptoms”. A range of similar major diagnostic features have been suggested. The current knowledge of MCS has been extensively reviewed in a textbook,¹⁵ in which it is stated “reference to rash is frequent, but presence of visible rash is less common”.

A phenomenon known as “low humidity occupational dermatoses,” with symptoms predominately associate with the skin, has been reported. In this case, the common exposure factor was a relative humidity at the lower end of the comfort range, around 35%. The problem was solved when the relative humidity was raised to 45–50%. The skin symptoms reported were pruritus and urticaria on covered areas and a scaling dermatitis on the face, scalp, and ears.^{16,17} Similar findings have been reported in patients living and working in air-conditioned houses when air humidity has been drastically reduced.¹⁸ Increased prevalence of dryness of the skin, eyes, nose, and throat has also been reported in clean rooms with moderate humidity.¹⁹

Because of the nonspecific nature of many symptoms reported in the office environment, it is often suggested that psychologic factors are responsible. They may even

TABLE 53-1—Common Symptoms Reported by Occupants of Buildings with Indoor Air Quality Problems (WHO)

Sensation of dry mucous membranes and skin
Erythema and itching
Eye, nose and throat irritation
High frequency of airway infections, and cough
Hoarseness, wheezing, and non-specific hypersensitivity
Mental fatigue and headache
Nausea and dizziness

be used as an excuse for incomplete investigations.²⁰ In a textbook on occupational dermatology, SBS is described as follows: "SBS...refers to epidemics of subjective symptoms (itching and burning sensations) without any clinically visible signs, which occur in the work environment. This situation can be related, for instance, to low relative humidity but may also represent a mass psychogenic illness."²¹ Experience gained from the investigation of 19 episodes of probable mass psychogenic illness (MPI) by the National Institute for Occupational Safety and Health (NIOSH) has been summarized.²² Although some symptoms typical of MPI are common to SBS, skin symptoms were not reported in these episodes. Signs suggestive of MPI, such as sudden onset of relatively severe symptoms, conversion symptoms, and recurrences in affected individuals when they congregate, make it possible to separate this phenomenon from real indoor air problems.²²

EPIDEMIOLOGY

The prevalence of SBS is not known, simply because there is no agreed definition of the syndrome. Most epidemiologic studies are cross-sectional and use questionnaires to record the prevalence of symptoms or combinations of symptoms compatible with the WHO list. Most studies look at selected populations while a few are general population studies. Some studies record "building-related" symptoms while others report symptoms independent of attribution. It has been shown that a considerable bias in attribution can result from the information given when collecting the data. In a Danish study, the prevalence rates of symptoms were similar, but reporting of work-relatedness and home-relatedness differed considerably between two study groups to which different information was given. If the information letter focused more on the workplace than the home, the subjects were more likely to report that their symptoms were work-related. Likewise, the subjects reported more home-related symptoms if focus was on the environment at home.²³

Work-related skin symptoms in office buildings in the UK (1984) have been reported with a prevalence ranging from 6–16% (dry skin), 2–3% (rash) and 3–7% (itchy skin) in buildings with different ventilation systems.²⁴ Swedish data (1993) from a random sample of office workers reported the prevalence of symptoms perceived every week independent of attribution.²⁵ Women reported higher prevalence than men (Table 53-2). A combination of at least one general, one mucosal (eye, nose, throat) and one skin symptom was perceived by 4% of men and 12% of women.

In a Japanese survey (2004) of newly built private homes, symptoms that occurred commonly or mainly in the home were recorded.²⁶ Skin symptoms (itching, dry, flushed, and erupted skin) were more prevalent in women (18%) than in men (11%). The German ProKlimA project (2004), involving 14 office buildings, reported at least one fairly or very annoying skin symptom (raw skin, irritated skin,

TABLE 53-2—Prevalence (%) of Symptoms Perceived Every week Among Men and Women in Office Work.²⁵

Symptom	Men (%)	Women (%)
Dry facial skin	8.1	24.4
Flushed facial skin	4.6	8.5
Itching/stinging/tight or burning sensations of facial skin	3.0	8.1
Scaling/itching scalp or ears	8.6	9.9

dry skin, red skin, itching skin, flaky skin, rash, spotty skin, or brittle nails) in 25% of the participants.²⁷ SBS, defined as at least two sub-scales (organ systems) having at least three items (symptoms) that were "a minor annoyance" or worse, was experienced by 44% of women and 26% of men.²⁸ In a Norwegian study (2003) of 32 office buildings without previously recognized indoor air problems,²⁹ the prevalence of facial skin symptoms perceived every week was very similar to the Swedish figures.²⁵ Dry skin was perceived by 8% of men and 22% of women, itching/scaling by 9% and 13%, flushing by 2% and 6% and a burning sensation by 2% and 7% respectively. Swedish population data (2006) from the general population³⁰ show prevalence of skin symptoms (independent of attribution) of the same magnitude but somewhat lower than in a population of office workers.²⁵ Dry facial skin was perceived every week by 8% of men and 18% of women, flushed facial skin by 4% and 5%, facial sensory skin symptoms by 2% and 3% and body itching without any rash by 3% and 5% respectively. There is seasonal variation in SBS symptom reports³¹ and most studies on indoor climate and symptoms are performed during the cold season when symptoms are most prevalent.

Because of the nonspecific nature of SBS symptoms, epidemiologic studies have an in-built weakness. One can assume that a certain proportion of reported SBS symptoms are associated with IAQ problems, otherwise the linear relationship between symptom reports and ventilation rates could not have been established. On the other hand, it is likely that an unknown proportion of reported symptoms have causes other than IAQ. This latter proportion leads to a misclassification in prevalence studies and risk assessment studies in which the health outcome is established using questionnaires. If this misclassification is independent of the factors/characteristics (for example gender, age, psychosocial stress, ventilation and volatile organic compound levels) in relation to which the outcome is analyzed, then this misclassification will cause a lower precision in the estimates but will not bias the results. If the health outcomes could have been defined more specifically for IAQ problems, then the associations found would have been even stronger than those reported. In questionnaire studies, alternative causes for the symptoms are difficult to rule out. However, in most risk assessment studies atopy or atopic dermatitis have been adjusted for.⁹

In most studies, either the work environment or the home environment has been investigated. However, in a few studies, there have been attempts to include both environments. In some work-place investigations, surrogate variables for the home environment have been used instead of actual measurements in individuals' dwellings. One common surrogate variable for ventilation rate is the presence of condensation on windows during winter time in cold or temperate climates.^{9,32}

CLINICAL COURSE/PROGNOSIS

While some reviews have stated that SBS is characterized and even defined by the relief of symptoms when the affected person leaves the building,³³ others have pointed out the gradual onset and long duration of the symptoms even in early descriptions of the syndrome.^{8,34} In fact, there are no studies supporting the statement that SBS symptoms always resolve immediately after exposure ceases. There is however, evidence for long-lasting symptoms in a study showing slowly decreasing mucosal hyperreactivity, years after working in a school with moisture problems.³⁵ A follow-up study of the prevalence of work-related SBS symptoms among office workers, reported a decrease in symptom prevalence soon after moving to a building with an improved ventilation system. Three years later, however, nearly half of the symptom prevalence remained.³⁶ In the first follow-up study of SBS patients who had previously been referred to hospital, it was shown that symptoms decreased over time. Nearly half of the patients claimed that symptoms were more or less unchanged after 7 years or more, despite actions taken to mitigate them.³⁷ In the same study the most prevalent environmental factors triggering skin symptoms were: the use of public transport, using photocopiers or printers, fluorescent lamp exposure and going to shopping malls.³⁷ Due to reported long-lasting symptoms in SBS patients triggered by other environmental factors, some authors consider that persistent SBS symptoms represent multiple chemical sensitivity (MCS).³⁸ The similarities between SBS and MCS have been pointed out in a recent textbook.³⁹

SKIN SYMPTOMS AND SIGNS

Clinical studies of SBS are sparse and it is sometimes stated that there are no clinical signs.^{21,33} One Swedish study is of particular interest, as it focuses on reactions in children and because it is one of the studies upon which the WHO list of SBS symptoms was based (Lindvall T, personal communication). During clinical examination, dry and erythematous skin on the face and extremities was more frequently found among children in day care centers with IAQ problems compared to control buildings.⁴⁰ Skin reactions in patients referred to a dermatology department because of symptoms perceived in buildings with indoor climate problems have been reported. Facial erythema,

rosacea, scaling of the scalp, ears and face, urticaria and "itching folliculitis" were common work-related findings.⁴¹ In the follow-up study of patients mentioned above,³⁷ the most common skin symptoms noted during the primary investigation in the hospital clinic were facial erythema and body itching. At follow-up, facial erythema was the dominant skin symptom. These two latter studies are the only ones where patients have been clinically examined and where alternative causes and diagnoses have been ruled out, for example by patch testing.

Skin reactions related to the indoor environment have been reviewed in a textbook,⁴² in which findings from the German ProKlimA study are noted. Questionnaire-reported symptoms were compared to medical observations and measurements of skin sebum content and the hydration of the stratum corneum. Individuals with low levels of sebaceous secretion and/or low stratum corneum hydration reported significantly more skin complaints.⁴³ In a case-referent study of SBS, two personal factors were significant risk indicators after adjustment for atopy: photosensitive skin and a strong "stinger test" reaction.³² As the study was cross-sectional, it was not possible to determine which came first, the SBS symptoms or the "stinger" reactivity.

SEARCH METHODOLOGY

Search Terms in Pub Med

Sick building, sick building syndrome (SBS), Nonspecific building-related symptoms, nonspecific building-related illness, building related illness (BRI), indoor air, indoor air quality (IAQ), indoor environment and skin, skin symptoms, skin signs, dermal symptoms, dermal signs, dry skin, itch, erythema, skin rash, rash, cutaneous symptoms, cutaneous signs, cutaneous manifestations

Handbooks

- Textbook of Clinical Occupational and Environmental Medicine, 2nd ed, (eds). Rosenstock L, Cullen MR, Brodkin CA, Redlich CA. Elsevier Saunders 2005.
- Environmental and Occupational Medicine, 4th ed. (eds). Rom WN, Markowitz SB. Lippincott Williams & Wilkins, Philadelphia, 2007.
- Indoor Air Quality Handbook, (eds). Spengler JD, Samet JM, McCarthy JF. McGraw-Hill, New York, 2001.

RESEARCH QUESTIONS AND ANSWERS

What is the definition of SBS? How is SBS diagnosed? Are there cutaneous manifestations in SBS? If yes, what are the manifestations and are these manifestations specific to SBS?

There is no agreed clinical definition of SBS. There are, however, a number of operational definitions of SBS and SBS symptoms used in epidemiologic studies. SBS cannot

be positively diagnosed based on clinical criteria. Building-related symptoms are diagnosed when a temporal relationship to spending time in a certain building is verified and when alternative explanations are ruled out.

There are cutaneous manifestations in SBS. Epidemiologic studies highlight perceived dry and erythematous facial skin as the dominant building-related symptoms, and the few clinical reports available refer to facial erythema as a typical finding.

The reported skin symptoms and signs are not specific to SBS. The few clinical tests that have been conducted on individuals with symptoms (sebum content, stratum corneum hydration and the "stinger test") have not been validated against other conditions and cannot be used for diagnosing building-related skin symptoms.

CONCLUSION

Sick building syndrome relates to a list of symptoms experienced by some individuals who spend time in buildings with IAQ problems; it is not a defined syndrome. There are a number of skin manifestations associated with other "SBS symptoms." Dry facial skin and facial erythema are the symptoms most often reported as "building-related". Dry facial skin may not only indicate exposure to low relative air humidity but also to polluted air. The symptoms are nonspecific and common in the general population. Even if building-related symptoms often abate soon after affected persons leave the building, the symptoms may become long-standing or chronic in some individuals.

Our review of reported skin reactions related to indoor climate factors indicates that the suggested "primary SBS symptoms", (i.e., perceived dryness of the skin and erythema) can trigger or aggravate a clinically observable disease in a number of predisposed individuals. In addition, skin signs may be more diverse than previously recognized. Moreover, the findings seen in clinical practice may reflect the impact of physical, chemical, and psychosocial factors interacting in a complex way.

There is a need for both epidemiologic and clinical studies to develop our understanding of skin reactions related to indoor air quality and of how skin symptoms and signs are connected to other SBS symptoms. Before questionnaire-based studies can be improved with more specific questions than those currently used, there is an urgent need for extensive case studies, which thoroughly examine subjects working or living in buildings with defined IAQ problems. This approach could establish whether there are core symptoms common to different IAQ problems and if there are symptoms specific to certain exposures. Risk assessment studies should also, as far as possible, include investigations of indoor environments where people spend most of their time (i.e., their work-places and their homes).

What We Know

- There is an association between low outdoor air flow rates and SBS symptoms.
- There is an association between psychosocial stress and SBS symptoms.
- SBS symptoms are more prevalent in women than in men.

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III

Risk Factor Analysis



Risk Factors for Nonmelanoma Skin Cancer

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Nonmelanoma skin cancer is the most common cancer in Caucasians. Cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) constitute nearly all non-melanoma skin cancers, the incidence of which tumors is rising.¹⁻³ Population-based studies demonstrate an increase in the incidence of nonmelanoma skin cancer among young women and men.^{2,4}

SCC has an incidence of 16 per 100,000 people in central Europe and of 356 per 100,000 sun-exposed Caucasians in the United States.⁵ Accounting for approximately 20% of cutaneous malignancies, squamous cell carcinoma (SCC) is the second leading cause of skin cancer in Caucasians.⁶ Cutaneous squamous cell carcinoma has significant adverse public health effects because of high medical costs and, in advanced or aggressive cases, compromised quality of life from devastating aesthetic and psychosocial sequelae, functional impairment, and other serious consequences.^{1,6-7}

The reported incidence of BCC varies among different countries from approximately 50 cases per 100,000 person-years in Finland,⁸ to 150 cases in UK⁹ and 935 in Australia respectively,¹⁰ while a recent prospective cohort study concluded that actual BCC tumor burden is much greater in the population than is apparent from normal incidence rates.¹⁰

The head and neck region is the most common skin location of nonmelanoma skin cancer development; up to 85% of basal cell carcinomas develop in the head and neck region.^{5,11}

A biomarker, or biologic marker, is in general a substance used as an indicator of a biologic condition. It is a characteristic that is objectively measured and evaluated as an indicator of normal biologic processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention. A risk factor is a variable associated with an increased risk of disease or infection. Risk factors are correlational and not necessarily causal, because correlation does not imply causation.¹²

In the last decade, new discoveries in cancer research generally and in nonmelanoma skin cancer research more specifically are targeted in finding new biomarkers of potential prognostic value, and in better understanding the pathophysiologic processes of the disease, to improve current therapies or introduce novel treatment

approaches.¹³ Human cells, in order to transform to cancer cells need to: (1) provide growth signals and obtain growth self-sufficiency, (2) ignore growth inhibitory signals, (3) avoid apoptosis, (4) replicate without limit, (5) sustain angiogenesis, and (6) invade and proliferate.¹⁴ While these are true for most cancers including nonmelanoma skin cancer; with regard to BCC, it is rather unlikely that (5) and (6) occur. The reason for that could be the low to nonexistent metastatic potential of BCC and the fact that the majority of tumors ulcerate in the center, thereby suggesting a limited ability to provoke and sustain angiogenetic molecular signalling.²

In this chapter, we describe risk factors for nonmelanoma skin cancer development, recurrence following treatment with curative intent, second primary nonmelanoma skin cancer tumors and metastasis of SCC tumors. In order for the chapter to be more comprehensive and practical for clinicians, it is structured along clinically relevant questions to which we provide evidence-based answers. These questions are:

1. Which patients are more likely to develop nonmelanoma skin cancer?
2. Are there any clinico-epidemiologic factors that predispose to nonmelanoma skin cancer development?
3. Are patients with prolonged Ultra Violet (UV) radiation exposure at higher risk of developing nonmelanoma skin cancer?
4. Are all patients equally prone to nonmelanoma skin cancer development when exposed to UV radiation?
5. Is UV exposure the only significant risk factor for nonmelanoma skin cancer development? Are there any genetic factors that predispose to nonmelanoma skin cancer development?
6. Which patients are more likely to develop second primary nonmelanoma skin cancer?
7. Which of those patients treated for nonmelanoma skin cancer are more likely to experience a recurrence?
8. Are there patients in higher risk for nonmelanoma skin cancer metastasis?
9. Does BCC metastasize? Are there patients in higher risk for BCC metastasis?

WHICH PATIENTS ARE MORE LIKELY TO DEVELOP NONMELANOMA SKIN CANCER?

Are There Any Clinico-Epidemiologic Factors that Predispose to NMSC Development?

Sex-Related Factors

Large epidemiologic studies concluded that age-standardized incidence rates of people with new histopathologically confirmed NMSC are on the rise.² These incidence rates for nonmelanoma skin cancer are reported to be higher in men,^{9,15} (Table 54-1). Of note, the mortality rate from nonmelanoma skin cancer is reportedly two-fold in men than in women.¹⁶

Age-Related Factors

Incidence rates are reported to be higher in the elderly.^{9,15} Epidemiologic studies have reported an increase in the incidence of nonmelanoma skin cancer in ages 30-39.^{9,4,17} A 27-year long prospective cohort study demonstrated a disproportionate increase in basal cell carcinoma in young women.⁴ Another single-center cohort study reported a significant trend towards superficial clinical type of BCC in younger patients. However, there is some inconsistency in the literature with regard to the latter argument.²

Dietary Factors

Reports from Australia state significantly reduced odds ratio for NMSC with higher category dietary fat intake using both case-control and cohort study designs.^{2,18} A recent cohort study, concluded that dietary fats are not associated with BCC occurrence¹⁹ in consistence with recently published results stating lack of efficacy of antioxidant supplements from a randomized clinical trial. (NCT00272428).²⁰

However, in participants of the Nambour Skin Cancer Prevention Trial with a history of skin cancer, total fat intake was associated with increased numbers of SCC tumors comparing the highest to lowest tertile.¹⁹ The same trial demonstrated a decreased risk of SCC tumors for high intakes of green leafy vegetables and an increased risk for high intake of unmodified dairy products.²¹ High meat and fat-consuming patterns were positively associated with development of SCC tumors after adjustment for confounders and even more strongly associated in participants with a skin cancer history (see Table 54-1).²²

In a random sampling case control study from the Southeastern Arizona Skin Cancer Registry, increased levels of arachidonic acid in red blood cell membranes were associated with increased risk of SCC and this association remained significant when controls with actinic

keratosis precursor lesions were excluded. SCC risk was highest among the upper quartile of arachidonic acid content in red blood cell membranes. In contrast, increasing proportions of palmitic acid and palmitoleic acid in red blood cell membranes were associated with reduced SCC risk (see Table 54-1).²³

BODY MASS INDEX

No significant association was found between any of the anthropometric measures or indices and risk of NMSC after controlling for potential confounding factors including sun exposure. Short-term weight gain has been suggested to increase the risk of developing NMSC in the female population.²

Drug-Related Factors

A randomized clinical trial (RCT) reported a weak and inconsistent chemopreventive effect of non-steroid anti-inflammatory drugs (NSAIDs) on NMSC development (see Table 54-1).²⁴ Significant positive associations were observed between total alcohol intake and risk of BCC in cohort studies.² A case-control study found that history of regular tea consumption was weakly associated with increased BCC risk after adjustment for age and sex, but the study could have been susceptible to recall bias and to confounding by potential unknown cancer risk factors associated with tea consumption.² Oppositely, having ever consumed tea regularly was reported to be associated with a significantly lower risk of SCC.²⁵ A randomized clinical trial proved that selenium supplementation is ineffective in preventing basal cell carcinoma. In the same trial after a 10-year follow up period, selenium supplementation was associated with statistically significantly elevated risk of squamous cell carcinoma and of nonmelanoma skin cancer.²⁶ Beta carotene supplementation had no effect on the incidence of a first nonmelanoma skin cancer after adjusting for age and randomized aspirin assignment.²⁷

Recently, FDA security files revealed that some new hypnotics may increase nonmelanoma skin cancer risk. However, currently available evidence only derives from rodent experimental models.²⁸

A meta-analysis of case-control and cohort studies demonstrated that Vitamin D supplementation did not confer any preventive benefit with regard to NMSC development. However, no clear pharmacogenomic benefit from Vitamin D supplementation was reported for patients bearing specific mutations in the vitamin D receptor (VDR) gene (FokI and BsmI polymorphisms).²⁹ In contrast, the VDR Bsm1 BB genotype was significantly associated with an increased SCC risk. An unfavorable pharmacogenomic interaction between the VDR Bsm1 polymorphism and total vitamin D intake was observed for SCC, where the highest risk was reported in women with the BB genotype

(Continued on following page 857)

TABLE 54-1—“Which Patients are More Likely to Develop NMSC?” Risk Factors for Incidence of NMSC

Citation	Design	Patients	Risk Factor	NOS Scale Scores		
				Selection Comparability	Outcome Comparability	Clinical importance
(Grau et al., 2006)	RCT	1,805 subjects with a recent history of NMSC were randomized to placebo or 50 mg of daily beta-carotene	Use of NSAIDs in the year previous to diagnosis	SCC (adjusted): OR=0.71, 95%CI: 0.48-1.04		To detect patients in higher risk of developing SCC
(Duffield-Lillico et al., 2003)	RCT	1312 patients	Selenium supplementation	SCC: HR=1.25, 95% CI: 1.03-1.51 NMSC: HR=1.17, 95% CI: 1.02-1.34		To detect patients in higher risk of developing NMSC
(Levine et al., 1997)	RCT	525 participants with a history of at least four basal cell carcinomas (BCCs) and/or cutaneous squamous cell carcinomas (SCCs)	Isotretinoin group compared with placebo	SCC: HR=1.79, 95% CI: 1.16-2.76		To detect patients in higher risk of developing SCC
(Harris et al., 2005)	Case Control study	Participants randomly selected from the Southeastern Arizona Skin Cancer Registry	Increased levels of arachidonic acid in RBC membranes (each mg/100 mL change)	SCC: OR=1.08; 95% CI: 1.02-1.15	4	To detect patients in higher risk of developing SCC
			Patients among the upper quartile of arachidonic acid	OR=2.38; 95% CI: 1.37-4.12	2	
			Increasing proportions of palmitic acid (each mg/100 mL change)	OR, 0.94; 95% CI, 0.89-1.00	3	
			Increasing proportions of palmitoleic acid (each mg/100 mL change)	OR, 0.49; 95% CI, 0.30-0.81		
(Stacey et al., 2008), (Stacey et al., 2009)	Genome-wide SNP association study	930 Icelanders with BCC and 33,117 controls	Gene & Polymorphism: BCC1 rs7538876 BCC2 rs801114 BCC4 rs11170164 BCC5 rs2151280[C] BCC6 rs157935[T]	3	2	To detect patients in higher risk of developing BCC

(Continued)

TABLE 54-1—"Which Patients are More Likely to Develop NMSC?" Risk Factors for Incidence of NMSC (*Continued*)

Citation	Design	Patients	Risk Factor	Efficacy	NOS Scale Scores		Clinical importance
					Selection	Comparability	
(Rafnar et al., 2009)	Genome-wide SNP association study	930 Icelanders with BCC and 33,117 controls	Gene & Polymorphism: BC3 rs401681	BCC: OR=1.25, p<0.0001	3	1	3 To detect patients in higher risk of developing BCC
(Han et al., 2006b)	Nested case control study	286 squamous cell carcinomas, 300 basal cell carcinoma and 873 controls	Gene & Polymorphism: MC1R 151 cys polymorphism	BCC: OR=1.56, 95% CI:1.03-2.34 SCC: OR=1.67 95% CI: 1.12-2.49	3	1	3 To detect patients in higher risk of developing NMSC
(Han et al., 2009)	Case control study	286 squamous cell carcinomas, 300 basal cell carcinoma and 873 controls	shorter telomere length	BCC: OR=1.85 95% CI: 0.94-3.62, p=0.09	3	1	3 To detect patients in higher risk of developing BCC
(Nan et al., 2009)	Case control study	286 squamous cell carcinomas, 300 basal cell carcinoma and 873 controls	Gene & Polymorphism: OCA2 Arg419Gln ASIP g.8818 A>G	BCC: OR=1.50, 95% CI: 1.06-2.13 SCC: OR=0.73, 95% CI: 0.53-1.00 TYR Ser192Tyr TYR haplotype carrying only the Arg402Gln variant allele	3	2	3 To detect patients in higher risk of developing NMSC
				SCC: OR=1.35, 95% CI: 1.04-1.74 Haplotype rs4911414[T] and rs1015362[G] near ASIP			
(Han et al., 2006a)	Nested case control study	286 squamous cell carcinomas, 300 basal cell carcinoma and 873 controls	Gene & Polymorphism: P53 Arg72Pro Pro/Pro polymorphism	BCC: OR=1.79, 95% CI:1.01-3.17	3	1	3 To detect patients in higher risk of developing BCC
(Han et al., 2007)	Nested case-control study	286 squamous cell carcinomas, 300 basal cell carcinoma and 873 controls	Gene & Polymorphism: VDR Bsm 1 BB genotype Interaction BB genotype and high vitamin D intake	SCC: OR=1.51, 95% CI: 1.00-2.28 OR=2.38, 95% CI: 1.22-4.62	3	1	3 To detect patients in higher risk of developing SCC

(Han et al., 2004b)	Nested case-control study	286 squamous cell carcinoma (SCC), 300 basal cell carcinoma (BCC), and 873 controls	Gene & Polymorphism: XRCC1 Arg194Trp wt/var XRCC1 Arg399Gln var/var	SCC: OR=1.51, 95% CI: 1.01–2.28 OR=0.61, 95% CI: 0.39–0.97	3	2	3	To detect patients in higher risk of developing SCC
(Han et al., 2004a)	Nested case-control study	286 squamous cell carcinoma (SCC), 300 basal cell carcinoma (BCC), and 873 controls	Gene & Polymorphism: XRCC3 18085T (241Met)	SCC: OR=0.69, 95% CI: 0.51–0.94, p=0.002	3	2	3	To detect patients in higher risk of developing NMSC
			BCC:	BCC: OR=0.67, 95% CI: 0.49–0.91, p=0.005				To detect patients in higher risk of developing BCC
			BCC:	BCC: OR=2.23, 95% CI: 1.18–4.19, p=0.007				To detect patients in higher risk of developing BCC
			BCC:	BCC: OR=1.72, 95% CI: 1.08–2.73				To detect patients in higher risk of developing BCC
			BCC:	BCC: OR=1.72, 95% CI: 1.08–2.73				To detect patients in higher risk of developing BCC
(Ibiebele et al., 2009)	Prospective cohort study	Nambour Skin Cancer Prevention Trial (participants with a history of skin cancer)	Total fat intake (comparing the highest to lowest tertile)	SCC (adjusted): RR=2.42, 95% CI: 1.20–4.88, p=0.01	3	2	3	To detect patients in higher risk of developing SCC
(Hughes et al., 2006)	Prospective cohort study	Nambour Skin Cancer Prevention Trial	High intakes of green leafy vegetables High intake of unmodified dairy products	SCC: RR=0.45, 95% CI: 0.22–0.91, p=0.02 RR=2.53, 95% CI: 1.15–5.54, p=0.03	3	2	3	To detect patients in higher risk of developing SCC
(Ibiebele et al., 2007)	Prospective cohort study	Nambour Skin Cancer Prevention Trial	Meat and fat patterns (total population) Meat and fat patterns (participants with skin cancer history)	SCC (adjusted): RR=1.83, 95% CI: 1.00–3.37, p=0.05 RR=3.77, 95% CI: 1.65–8.63, p=0.002	3	2	3	To detect patients in higher risk of developing SCC

(Continued)

TABLE 54-1—"Which Patients are More Likely to Develop NMSC?" Risk Factors for Incidence of NMSC (*Continued*)

Citation	Design	Patients	Risk Factor	Efficacy	NOS Scale Scores	Outcome	Clinical importance
(Suarez et al., 2007)	Multicenter case-control study	1333 basal cell carcinoma (BCC) and 183 squamous cell carcinoma (SCC) and 1507 controls	Miners and quarrymen Secondary education teachers Masons Railway engine drivers and firemen Specialised farmers Salesmen Miners and quarrymen Secondary education teachers Livestock, construction workers not elsewhere classified Stationary engine and related equipment operators not elsewhere classified Masons	NMSC: OR=7.04, 95% CI:2.44-20.31 OR=1.75, 95% CI:1.05-2.89 BCC: OR=1.54, 95% CI:1.04-2.27 OR=4.55, 95% CI:0.96-21.57 OR=1.65, 95% CI:1.05-2.59 OR=3.02, 95% CI:1.05-2.86 OR=7.96, 95% CI:2.72-23.23 OR=1.76, 95% CI:1.05-2.9 SCC: OR=2.95, 95% CI:1.12-7.74 OR=5.31, 95% CI:1.13-21.04 OR=2.55, 95% CI:1.36-4.78	2 2 1	2 2 1	To detect patients in higher risk of developing NMSC To detect patients in higher risk of developing BCC To detect patients in higher risk of developing SCC

(Thirumaran et al., 2006)	Case-control study	529 cases diagnosed with BCC and 533 controls from Hungary, Romania and Slovakia	Gene & Polymorphism: CC (XRCC3) / CC (NBS1) genotype compared to the TT (XRCC3) / GG (NBS1) genotype	SCC: OR=8.79, 95% CI: 2.10-36.8	3	2	2	To detect patients in higher risk of developing SCC
			BCC: NBS1 E185Q G>C polymorphism					To detect patients in higher risk of developing BCC
			BCC (Age and nationality adjusted): OR 8.79 (2.10-36.8)					To detect patients in higher risk of developing BCC
			Temperature effect on human skin cancer	BCC incidence was higher by 2.9% ($\pm 1.4\%$) per degree C	4	1	2	To detect regions where patients are in higher risk of developing BCC
(van der Leun et al., 2008)	Trohoc epidemiologic analyses	10 US regions	Gene & Polymorphism: ASIP polymorphism TYR R402Q polymorphisms	BCC: OR=1.33, p<0.001 OR=1.14, p<0.001	3	2	3	To detect patients in higher risk of developing BCCC
(Gudbjartsson et al., 2008)	Large scale case control study	2,163 BCC patients and over 40,000 controls	Male to Female (logit=female) Each year of follow up	BCC: RR=1.1, 95% CI: 1.06-1.14 RR=1.03, 95% CI: 1.01-1.04	3	2	3	To detect patients in higher risk of developing BCCC
(Bath-Hextall et al., 2007)	Observational trohoc	11,113 BCC patients	Patients with BCC/SCC were less likely to develop a further BCC	BCC: OR=0.31, 95% CI: 0.15-0.63, p=0.001	3	1	3	To detect patients in higher risk of developing BCCC
(Ramachandran et al., 2009)	Case control study	1040 patients who developed BCC only were compared with 140 patients who developed BCC and SCC	Lowest selenium concentrations at baseline (0.4-1.0 micromol/L), versus those with the highest serum selenium concentrations (1.3-2.8 micromol/L)	BCC (adjusted): RR=0.43, 95% CI: 0.21-0.86, p=0.02 SCC (adjusted): RR=0.36, 95% CI: 0.15-0.82, p=0.02	3	2	3	To detect patients in higher risk of developing NMSC
(van der Pols et al., 2009)	Prospective cohort study	485 adults from an Australian community	Regional Radiation Therapy	NMSC: RR=6.3, 95% CI: 3.5-11.3	2	1	2	To detect patients in higher risk of developing NMSC
(Perkins et al., 2005)	Multicenter cohort study	13,132 eligible CCSS participants, 213 have reported NMSC						(Continued)

TABLE 54-1—"Which Patients are More Likely to Develop NMSC?" Risk Factors for Incidence of NMSC (*Continued*)

Citation	Design	Patients	Risk Factor	Efficacy	Clinical importance
					NOS Scale Scores
				Selection Comparability	Outcome NOS Scale Scores
(Rademaker-Troger et al., 2009)	Population-based cancer registry	BCC (n = 1,641)	Male outdoor worker versus indoor	BCC: RR=2.9, 95% CI: 2.2-3.9 SCC: RR=2.5, 95% CI: 1.4-4.7	2 1 3 To detect patients in higher risk of developing NMSC
(Ramachandran et al., 2003)	Case-control study	846 unrelated, Northern European Caucasians (29–90 years at first presentation) with one or more histologically proven BCC	Male (logit Female) Skin type 1 (logit Skin type 2–4) CYP2D6 EM polymorphism (logit CYP2D6 HET/PM) VDR TT polymorphism (logit VDR Tt and tt)	BCC: OR=1.20, 95% CI: 1.03–1.40, p=0.022 OR=1.36, 95% CI: 1.10–1.69, p=0.004 SCC: OR=1.34, 95% CI: 1.11–1.62, p=0.002 OR=1.31, 95% CI: 1.04–1.64, p=0.022	3 2 3 To detect patients in higher risk of developing BCC
(Rees et al., 2007)	Population-based matched case-control study	770 individuals with BCC, 696 with SCC, and 715 age- and sex-matched control subjects	Ever having consumed tea regularly	SCC: OR=0.70, 95% CI: 0.53-0.92	2 2 2 To detect patients in higher risk of developing SCC
(Lovatt et al., 2004)	Observational cohort study	428 unrelated Northern European Caucasians (aged 18–94 years at first presentation)	Male sex (logit=female) Never sunbathing during the age range (logit=often): 20–39.9 years 40–59.9 years >60 years	BCC: OR=2.00, 95% CI: 1.16–3.45, p=0.01 SCC: OR=0.19, 95% CI: 0.08-0.48, p=0.001 OR=0.20, 95% CI: 0.08-0.49, p=0.001 OR=0.42, 95% CI: 0.18-0.94, p=0.04	2 1 2 To detect patients in higher risk of developing BCC

(Karakas et al., 2006)	Population-based case-control study	252 SCC case patients, 525 BCC case patients, and 461 control subjects	Detection of: HPV antibodies HPV types in genus beta HPV 5	BCC: OR=1.6, 95% CI: 1.2-2.3 OR=1.5, 95% CI: 1.0-2.1 OR=1.8, 95% CI: 1.0-3.1	2 2 2 To detect patients in higher risk of developing BCC
(Wang et al., 2007)	Hospital-based case-control study	146 with basal cell carcinoma (BCC) and 109 with squamous cell carcinoma (SCC) and 333 cancer-free controls	DRC below the controls' median value	BCC (adjusted): OR=1.62, 95% CI: 1.07-2.45 SCC (trend): OR=1.63; 95%CI: 0.95-2.79	2 2 2 To detect patients in higher risk of developing NMSC
(Lira et al., 2006)	Matched case-control study	107 cases with NMSC and 132 controls free from NMSC matched for type of transplanted organ, duration of transplantation, sex and age	Gene & Polymorphism GSTP1 *A	NMSC: OR=1.7, 95% CI: 1.1-2.5, p=0.017 NMSC: OR=0.3, 95% CI: 0.1-0.8, p=0.012 SCC: OR=0.1, 95% CI: 0.0-0.7, p=0.012	3 2 3 To detect patients in higher risk of developing NMSC
(Brudnik et al., 2008)	Case-control study	102 BCC patients and 123 controls	GSTM1 Val(I105) homozygous and CYP1A1 Val(462)	NMSC: OR=4.5, 95% CI: 1.1-21.4, p=0.03 SCC: OR=6.5, 95% CI: 1.4-34.4, p=0.01.	2 1 2 To detect patients in higher risk of developing NMSC
(Herrero et al., 2005)	Matched case-control study	170 liver transplant recipients	Gene & Polymorphism: MC1R 151 cys polymorphism	BCC: OR=3.3, p<0.05	2 1 2 To detect patients in higher risk of developing BCC
(Boyd et al., 2002)	Matched case-control study	30 BCC women patients and 30 sex, age, and skin type matched controls	Liver transplant recipients.	NMSC: RR: 20.26, 95% CI: 14.66-27.29	2 1 2 To detect patients in higher risk of developing NMSC
(Yin et al., 2002)	Clinic-based case-control study	70 BCC patients and 117 controls	Cigarette pack—years of smoking Blistering sunburns	BCC: Positively associated (p=0.045) Positively associated (p=0.028)	4 2 3 To detect patients in higher risk of developing BCC
			Gene & Polymorphism: RAI intron1(G)	BCC: Protective role (p=0.004)	2 2 3 To detect patients in higher risk of developing BCC

(Continued)

TABLE 54-1—“Which Patients are More Likely to Develop NMSC?” Risk Factors for Incidence of NMSC (Continued)

Citation	Design	Patients	Risk Factor	Efficacy	Outcome	NOS Scale Scores	Clinical importance
(Yengi et al., 1996)	Case-control study	9 BCC patients and 11 controls	Gene & Polymorphism: GSTM3 AA polymorphism in combination with Skin type 1 GSTM1 null polymorphism CYP1A1 (locus 15q22-q24) m1m1 polymorphism	BCC: RR=2.06, p<0.001 RR=1.61, p<0.001 RR=1.47, p<0.001	3 2 3	To detect patients in higher risk of developing BCC	

OR=Odds Ratio; RR=Relative Risk; HR=Hazard Ratio trohoc=retrospective cohort study. BCC1=Basal Cell Carcinoma. Susceptibility to 1, locus 1p36 BCC-2=Basal Cell Carcinoma, Susceptibility to 2; locus 1q42. BCC3=Basal Cell Carcinoma, Susceptibility to O, 3; locus 5p15.33, BCC4=Basal Cell Carcinoma, Susceptibility to 4; locus 12q13, BCC5=Basal Cell Carcinoma, Susceptibility to 5; locus 9p21, BCC6=Basal Cell Carcinoma Susceptibility to, 6; locus 7q32, MC1R=Melanocortin 1 receptor; ASIP=Agouti signalling protein; TYR=Tyrosinase; NBS=Niemeggen breakage syndrome; XRC3=X-ray repair complementing defective in Chinese hamster 3; RAI=Retinoic acid induced gene; GSTM3=Glutathione S-transferase mu-3; GSTM1=Glutathione S-transferase mu-1; CYP1A1=Subfamily I, polypeptide 1; CYP2D6=cytochrome p450 subfamily II D polypeptide 6; VDR=Vitamin D receptor; DRC=DNA repair capacity

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and high vitamin D intake (see Table 54-1).³⁰ Thus, vitamin D supplementation is to date of no value in the prevention NMSC.

A number of ongoing trials study the preventive actions of a series of retinoids in NMSC. However the risk of a new SCC in was significantly increased in the isotretinoin group compared with placebo.³¹

Demographic Factors

In contrast to the Caucasian population, squamous cell carcinoma is the most common nonmelanomatous skin tumor in the African-American population.³² According to the public perception of UVR-induced skin cancer, populations or occupations with higher UVR exposure are anticipated to express higher risk for NMSC. Indeed, there are large-scale epidemiologic studies, which have found that the incidence rate of nonmelanoma skin cancer increased from the northern to the southern states.²

Occupational Factors

Elevated risks for NMSC have been reported among groundskeepers, gardeners, garage and service station-related occupations and to a limited extent among food industry occupations. Women in health services occupations were also reported to exhibit elevated risk for nonmelanoma skin cancer development.² In addition, constitutional susceptibility was reported to be an independent risk factor for BCC. On the contrary, epidemiologic studies reported the incidence rate for BCC to be higher in urban than in rural regions. Farmers, forestry workers, and fishermen demonstrated low incidence of BCC, whereas occupations with high level of education or compulsory health check-ups as well as medical care occupations appeared to have an increased incidence of BCC. The authors did not comment on whether this reversed risk could be attributed to regular follow-up or patients' self-reporting.² Results for the HELIOS-I multicenter case control study reported that concerning nonmelanoma skin cancer as a whole (both histologic types), miners and quarrymen, secondary education teachers, and masons registered exhibit excess risk, regardless of exposure to solar radiation and skin type. Frequency of BCC proved higher among railway engine drivers and firemen, specialized farmers and salesmen, in addition to miners and quarrymen and secondary education teachers. The occupations that registered a higher risk of SCC (though not of BCC) were those involving direct contact with livestock, construction workers, stationary engine and related equipment operators and masons (see Table 54-1).³³

Chronic exposure of radiologists to ionizing radiation at low to moderate levels was reported able to increase the risk of BCC but not of SCC, and this risk may be related to pigmentation characteristics.²

Immunocompromised Patients, Transplant Recipients and Irradiation Treated Patients

The remarkable improvement in immunosuppressive therapy and surgical procedures for organ transplantation observed since the first successful kidney transplant was achieved in 1954, now allows many organ types including kidney, heart, liver, lung, skin, cornea and bone marrow to be successfully transplanted.^{3,4-36} The survival of patients has increased substantially and it has also become clear with time that recipients present a higher risk of cardiovascular disease, infection and cancer.^{34,37} Renal transplant recipients (RTRs) submitted to lifelong immunosuppression, constitute the most important group of patients with long-term survival to have provided important information on the increased susceptibility to cancer. The cumulative risk of tumor development, which includes skin cancers, lymphomas and kaposi's sarcoma is reported to be 14% in the first 10 years after transplantation and increases to 40% at 20 years compared to 6% in the general population.³⁷ Half of the tumors are nonmelanoma skin cancers, predominantly squamous cell carcinomas, in contrast to the normal population where basal cell carcinomas prevail. The rapidly growing numerous NMSC, at multiple sun-exposed body sites in RTRs, are more aggressive and present increased metastatic potential resulting in substantial morbidity with increased mortality.^{34,37}

A retrospective cohort study of 926 kidney transplant recipients reported a 9.7% incidence of nonmelanoma skin cancer lesions with a median time of development of a first nonmelanoma skin cancer lesion of 4 years. Reported risk factors for nonmelanoma skin cancer among kidney transplant recipients include older men (>45 years), a history of post-transplant warts and longer duration of residence in a northern climate.³⁵ Another study estimated the relative risk of nonmelanoma skin cancer among liver transplant recipients to be twenty-fold as compared to sex- and age-matched population (see Table 54-1).³⁶

Patients who undergo radiation therapy also exhibit elevated risk for NMSC development.² Among participants of the Childhood Cancer Survivor Study the median age of occurrence was 31 years (range, 7 to 46 years). Location of nonmelanoma skin cancer included head and neck (43%), back (24%), chest (22%), abdomen and pelvis (5%), extremity (3%), and unknown (4%). Ninety percent of patients had previously received radiation therapy (RT); 90% of tumors occurred within the RT field. RT was associated with a 6.3-fold increase in NMSC risk (see Table 54-1).³⁸ Of note, a retrospective cohort study reported that BCC in irradiated scalp had a more aggressive behavior that might oblige for a more extended surgical resection.²

Infection-Related Factors

Cutaneous human papilloma virus (HPV) may be associated with the development of nonmelanoma skin cancer, as

suggested by reports of HPV DNA in nonmelanoma skin cancer tumors. HPV DNA was detected in various skin lesions including basal cell carcinomas, actinic keratoses, and SCC.³⁷

Human papilloma virus DNA is reported to be commonly expressed in superficial layers of BCC lesions, but is not necessarily present throughout tumors.² A population-based case-control study that detected HPV antibodies reported no difference in HPV seropositivity between BCC patients and controls.²

When SCC is concerned, most reports did not point to any significant association with HPV infection.³⁹ However, Karagas et al. detected HPV antibodies more frequently in SCC patients than in control subjects. Among different HPV types, seropositivity to HPV types in genus beta, particularly HPV 5, was associated with SCC risk (see Table 54-1). Individuals with tumors on chronically sun-exposed sites were more likely to be seropositive for beta HPV types than individuals with SCC at other anatomic sites.⁴⁰

Are Patients With Prolonged UV Exposure at Higher Risk of Developing NMSC? (Ultra Violet Radiation Related Factors)

Extrinsic skin aging or ‘photoaging’, as opposed to intrinsic skin aging, is the result of exposure to external factors, mainly ultraviolet irradiation.⁴¹ It appears that photoaging is predisposing to NMSC development: Photoexposed skin areas account for 92.6% of NMSC tumors. A positive association between sensitivity to sunburn and increased risk for NMSC development has been reported for NMSC of the head but not for NMSC of the trunk. Patients reported to having red hair; green, hazel, or blue eyes; a tendency to sunburn; and north European ancestry were reported to have elevated risk for NMSC development. Keratotic skin lesions were reported to be associated with NMSC and have been proposed as a potential prognostic criterion for identifying those organ-transplant recipients with an increased risk for skin cancer development, who should be offered more intensive skin surveillance.² The lifetime number of blistering sunburns was also found to be positively associated with NMSC risk.² Skin type 1 patients were reported to be more prone to development of NMSC.⁴² Men who as teenagers had been outdoors on a daily basis were reported to have elevated risk for NMSC when compared to men who as teenagers had been outdoors less than once a week. Living in a residential area with high solar exposure as an adult was also found associated with an increased risk for NMSC, whereas living in such a region only during childhood was not found to increase NMSC risk.² Sunbathing was reported to be associated with a five-fold increased risk of truncal BCC but not with BCC histology⁴³ (see Table 54-1). Higher sun exposure while wearing a bathing suit was reported to be an independent risk factor for NMSC.⁴³⁻⁴⁴ Repeated exposure to tanning beds might also

be a contributory factor.⁴⁵ Sunscreen treatment was not reported to be associated with early or late first occurrence of NMSC. Multivariate hazard models of follow-up data from the Nambour Skin Cancer Prevention Trial revealed a trend towards a lower risk of subsequent NMSC tumors among a sunscreen intervention group.² Randomized-controlled trials concluded that regular application of sunscreen has no clear benefit in reducing risk for NMSC development (see Table 54-1).³⁴

It appears that the total amount of UV dose is associated with different forms of NMSC. A cohort study found the BCC to SCC ratio to be increased in participants who received low and medium UV doses while it was reduced for those who received very high UV doses. A very high UV dose was also associated with the doubling of the total number of tumors per person and a significantly increased risk of having SCC (see Table 54-1).⁴⁶ These results suggest that the association between risk and UV exposure is less dose-responsive in BCC than in SCC.

Are All Patients Equally Prone to NMSC Development if Exposed to UV Radiation? Which are the Predisposing Factors for Such a Patient to Develop NMSC? (Factors related to defective host response to ultraviolet radiation)

DNA-Repair

Exposure to UVR, specifically UVB, induces covalent bonds in DNA between adjacent pyrimidines, generating photoproducts such as cyclopyrimidine dimers (TT) and pyrimidine lesions, which are mutagenic if not repaired. Polymorphisms in the melanocortin 1 receptor (MC1R, locus 16q24.3) have been shown to be strongly associated with skin type.⁴⁷ Variant alleles have also been found to be strongly associated with red hair and experimentally assessed UVR sensitivity.

A nested case-control study suggested that MC1R gene variants were an important independent risk factor for nonmelanoma skin cancer. Information on MC1R status was reported to contribute up to a 3.3-fold increase in BCC risk (see Table 54-1).⁴⁷⁻⁴⁸ Specific SNPs at the tyrosinase (TYR, locus 11q1 4-q21) gene was reported to be associated with increased risk for SCC development⁴⁹ while two other SNPs, in the oculocutaneous albinism type II (OCA2, locus 16q24.3, 15q11. 2-q12) and in the agouti signalling protein (ASIP, locus 20q11.2) have been associated with increased BCC risk. The haplotypes rs4911414[T] and rs1015362[G] near the ASIP gene was also associated with higher SCC risk.⁴⁹

CpG sites are regions of DNA where a cytosine (C) nucleotide occurs next to a guanine (G) nucleotide in the linear sequence of bases along its length. Cytosine (C) to Thymidine (T) transitions at CpG sites adjacent to

pyrimidine-pyrimidine (PyPy) sequences were reported to be more prevalent in tumors from UV-exposed than UV-shielded body areas. CpG-mutations at non-PyPy sequences were reported to be more prevalent in tumors which received cumulative ionizing radiation (IR) dose higher than 1 Gy compared to those who received cumulative dose lower than 0.2 Gy. These data could be of potential use in determining the specific risk for BCC development among different persons or different body sites of a person when exposed to IR.²

A haplotype near agouti signalling protein (ASIP, locus 20q11.2) known to affect a similar spectrum of pigmentation traits as the MC1R variants was recently found to confer significant risk of BCC (OR = 1.33, p<0.001)⁵⁰ (see Table 54-1). Nevertheless, the ASIP polymorphism is not uniformly reported to be associated with BCC.⁴⁸ The results concerning MC1R and ASIP polymorphisms, were reported to be independent of the subjects' pigmentation characteristics⁴⁸ thus adding value to their potential use as biomarkers. Another polymorphism in tyrosinase (TYR, 11q1 4-q21) encoding the R402Q amino acid substitution, which was previously shown to affect eye color and tanning response, was also found to confer risk of BCC (see Table 54-1).⁵⁰

DNA repair capacity (DRC) was measured in the subjects' peripheral blood lymphocytes by using a host-cell reactivation assay that measures cellular activation of a reporter gene irradiated with UV light. Elderly BCC patients were reported to demonstrate a higher DRC compared to younger BCC patients and non-BCC controls. The effects of age, family history of skin cancer, and current sun exposure may confound such results and therefore DRC measurement is unlikely to become a useful routine predictor before the latter confounding associations are clarified.² Overall, there was a statistical significant 16% reduction in DRC in nonmelanoma skin cancer patients compared to controls. DRC below the controls' median value was associated with increased risk significantly for BCC but borderline for SCC after adjustment for age, sex, and other assay-related covariates (see Table 54-1).⁵¹ Because the association between risk and UV exposure is less dose-responsive in BCC than in SCC, suboptimal DRC may play a more important role in the etiology of BCC when the level of UV-induced DNA damage is low. Wang et al. observed that patients who had a BCC or single and nonaggressive nonmelanoma skin cancer tended to have the lowest DRC. Likewise, they observed the highest frequencies of UV-induced chromosomal aberrations in BCC patients, suggesting a major role of suboptimal DRC in the etiology of single nonmelanoma skin cancer. When the level of UV-induced DNA damage was high or accumulated because of chronic exposure to sunlight as seen in SCC, the DRC may be up-regulated; however such an adaptive increase in DRC in response to damage to DNA appeared to be overwhelmed by high levels of UV-induced damage, thus being associated with a high risk of SCC.⁵¹

Nucleotide excision repair (NER) is instrumental in removing DNA lesions caused by ultraviolet (UV) radiation,

the dominant risk factor for nonmelanoma skin cancer. Studies have examined polymorphisms in genes associated with DNA repair and identified significant associations with both xeroderma pigmentosum complementation group D (XPD, locus 19q13.2-3, also known as ERCC2) and x-ray complementing defective in Chinese hamster 3 (XRCC3, locus 14q32.3) genes, but not with any of five common haplotypes of excision repair complementing defective in Chinese hamster 1 (XRCC1, locus 19q13.2-q13.3) gene.² Another study reported the XRCC1 Arg194Trp het genotype to confer an increased risk for SCC development and the XRCC1 Arg399Gln var/var genotype to confer a reduced risk for SCC development.⁵² The variant allele for susceptibility to breast cancer T241M (C>T) polymorphism in the XRCC3 gene was associated with a decreased BCC risk⁵³ (see Table 54-1). The XRCC3 18085T (241Met) allele and its associated haplotype were significantly inversely associated with the risks of SCC and BCC (see Table 54-1). The XRCC3 4552C allele along with its associated haplotype and the XRCC2 30833A allele were significantly associated with increased BCC risk.⁵⁴

Another study supported the hypothesis that alleles of several polymorphisms in the chromosomal region 19q13.2-3, encompassing the genes retinoic acid-induced gene 1 (RAI, locus 19q13.2) and XPD, are associated with occurrence of basal cell carcinoma in Caucasian Americans.⁵⁵ Some authors have indicated that a specific haplotype partly defined by the alleles of three single nucleotide polymorphisms, RAI intron1(G), RAI exon6(T), and XPD exon 6(C), is associated with a protective gene variant in a region spanning from XPD to XRCC1⁵⁵ (see Table 54-1). Other authors suggested a role of the double-strand break (DSB) repair complex in BCC development. Genotyping of 19q13.2-3 and 14q32.3 regions to scrutinize for protective haplotypes could be of value in determining follow up strategy (see Table 54-1).

The A23G polymorphism present in xeroderma pigmentosum gene (XPA, locus 9q22.3) was associated with an increased risk of BCC and this polymorphism appeared to be a determining polymorphism in XPA that alters cancer susceptibility. A case control study investigated the effect of the A allele of the XPA gene adjusted for age, gender, pigmentation factors and severe sunburns in Caucasians. Using GG as the reference allele, the A allele was less frequent among cases of BCC and SCC⁵⁶ than controls. Risk from three or more severe sunburns was reported elevated only for those with the GG genotype. These results only exhibit a trend because they were significant at the 0.10 alpha level.² Men but not women homozygous for the C-allele for E185Q (G>C) polymorphism in the p95 protein encoding gene of the MRE11/RAD50 complex (also reported as Nijmegen breakage syndrome, NBS1, locus 8q21) showed an increased BCC risk. In men, the age and nationality adjusted odds ratio for the CC (XRCC3)/CC (NBS1) genotype was almost nine-fold compared to the TT (XRCC3)/GG (NBS1) genotype.⁵³ Moreover, the risk of multiple BCC was significantly

lower among variant allele carriers than in non-carriers (see Table 54-1).⁵³ Overall, these findings could allow for identification of patients with high risk to develop second primary BCC, should genotyping be used as a standard procedure. The same associations imply that BCC patients have a reduced capacity to repair UV-induced DNA lesions and are therefore more susceptible to UV-induced DNA damage in comparison to the general population.

Chemical Detoxication

Unlike UVB, UVA may have effects that are more indirect in DNA through ROS. UVR is also a local immunosuppressant for skin, giving rise to the suggestion that this may compromise local antitumor activity. The functional V16A polymorphism in the manganese superoxide dismutase gene (MNSOD, locus 6q25.3) was not found to be associated with skin cancer risk. Similarly, the polymorphisms C677T and A1298C in the methylenetetrahydrofolate reductase gene (MTHFR, locus 1p36.3) and the polymorphisms Fok1, Bsm1 and Cdx2 in the vitamin D receptor gene (VDR, locus 12q12-q14) did not point to any clinically significant association with increased nonmelanoma skin cancer risk in a nested case-control study.²

Associations between polymorphisms in the cytochrome p450 (CYP) and glutathione S transferase (GST) supergene families and BCC risk have been proposed.² Genes in both these families are involved in detoxification of various mutagens, while some GST members also detoxify the products of oxidative stress. Studies have shown that polymorphisms in glutathione s-transferase mu-1 (GSTM1, locus 1p13.3), GLUTATHIONE glutathione s-transferase theta-1 (GSTT1, locus 22q11.2) and cytochrome p450 subfamily II D polypeptide 6 (CYP2D6, locus 22q13.1) genes are associated with patients who present with multiple BCC. Another GST family member, glutathione s-transferase mu-3 (GSTM3, locus 1p13.3) was also found to be associated with multiple BCC⁵⁷ (see Table 54-1), thus, it could be of value in detecting multiple BCC patients. NAD(P)H dehydrogenase quinone 1 (NQO1, locus 16q22.1) gene null, GSTM1 B and GSTT1 null, and CYP2D6 EM polymorphisms have been reported to be associated with multiple BCC, although quantitative effects analysis showed that predisposition to many BCC is determined by an unknown number of further loci. The relative influence of NQO1 null was studied in a multivariate model adjusted for GSTM1 B, GSTT1 null, CYP2D6 EM, GSTM3, cytochrome p450 subfamily I polypeptide 1 (CYP1A1, locus 15q22-q24) gene and MC1R. NQO1 null and MC1R asp294/asp294 were reported to be associated with multiple BCC, and the association with CYP2D6 EM approached significance. Male gender, skin type 1, CYP2D6 EM and VDR TT genotypes were reported to be associated with more BCC per year with univariate analysis⁴² (see Table 54-1). Different factors mediate the numbers of BCC

per year in males and females and the univariate contributions of variables to risk were modest.⁴²

Allele GSTP1*A was associated with a higher risk of nonmelanoma skin cancer. Homozygosity for allele GSTP1 Val (105) was associated with reduced risk for NMSC development (see Table 54-1). Analysis of interactions between allelic variants showed a significant association between combined GSTM1 and CYP1A1 Val (462) genotypes, where individuals homozygous for the risk allele GSTM1 null and carrying also the allele CYP1A1 Val (462), showed a higher risk of developing nonmelanoma skin cancer.⁵⁸

Immunologic Effects

Exposure to UVR results in a cascade of events including a T-lymphocyte-mediated immunosuppression. DNA damage and the UVR-induced transformation of cis-urocanic acid (cUCA), can result in altered expression of several cytokines including tumor necrosis factor (TNF) TNF-alpha, interleukin (IL) IL-10, IL-1 α and β , IL-3, IL-6, IL-8, granulocyte-macrophage colony-stimulating factor, and nerve growth factor which results in an alteration from a T helper 1 to a suppressive T helper 2 response, thereby inhibiting the ability of antigen-presenting cells (APC) to induce antitumor immunity.² Of note, higher levels of cUCA were detected in SCC biopsies (44% of total UCA) compared to samples of BCC and that of healthy photoexposed skin (30%).⁵⁹ On the other hand, BCC situated on the head and neck was reported to over express certain Th2 cytokines, namely IL-4 and IL-5 and TNF-alpha.⁶⁰

Immunosuppressed transplant patients are reported to have a considerably higher risk for BCC, demonstrating a critical role for the immune system in BCC development.² It has been reported that the TNF allele (locus 6p21.3) haplotype a 2-b4-d5 statistically significantly influenced BCC numbers (mean BCC number, 8.1 vs. 3.7 in other allele combinations) in patients with multiple BCC (Table 54-2). A single base pair polymorphism at position -308 in the promoter region of the TNF-alpha gene associated with an enhanced secretion of TNF-alpha has been identified in humans. Mononuclear cells from patients with a previous BCC demonstrated a significantly increased release of TNF-alpha upon stimulation with lipopolysaccharide compared to mononuclear cells from age-matched control subjects.² TNF-alpha GG genotype was associated with more BCC per year.⁴² Additionally, HLA-DR4 (locus 6p21.3) was reported to be associated with multiple BCC, however authors concluded that HLA-system might only play a minor role in the development of multiple BCC. Furthermore, GSTM1 and GSTT1 genotypes have been shown to influence the inflammatory response following UVR exposure, a finding possibly reflecting the link between oxidative stress and immune function.² Overall there is sufficient evidence to support that immunologic status plays some role in the development of NMSC but to date limited biomarkers could be of prognostic value (see Table 54-2).

TABLE 54-2—“Which Patients are More Likely to Develop Second Primary Nonmelanoma Skin Cancer (NMSC)?” Predictors for Multiple Tumor Development in Nonmelanoma Skin Cancer Patients

Citation	Design	Patients	Predictors	Efficacy	NOS Scale	Outcome	Clinical importance	
(Marcil & Stern, 2000)	Meta-analysis	26 studies including 4 that specifically quantified the risk of an NMSC of any type after an NMSC	Having experienced at least one BCC	BCC: 3-year cumulative risk 44% SCC: 3-year cumulative risk 6%			To detect patients in higher risk for second primary tumor development after treatment with curative intent	
(Ramachandran et al., 2009)	Observational retrospective cohort study	1040 patients who developed BCC only were compared with 140 patients who developed BCC and SCC	Having experienced one SCC	BCC: OR=0.31, 95% CI: 0.15–0.63, p=0.001 SCC: 3-year cumulative risk 18%	3	2	To detect patients in higher risk for SCC development after diagnosed with BCC	
(Graells, 2004)	Observational retrospective cohort study	535 patients with 829 BCC, 85 SCC and 28 actinic keratoses.	Patients with history of BCC and SCC versus patients with history of BCC only	Male sex (logit=female) Each tumour at first diagnosis Each year of older age at first diagnosis	RR=1.89, 95% CI: 1.29–2.79, p<0.001 RR=1.21, 95% CI: 1.11–1.31, p<0.001 RR=1.02, 95% CI: 1.00–1.03, p=0.024	3	2	To detect patients in higher risk for second primary tumor development after treatment with curative intent
(Ramachandran et al., 2000)	Case-control study	457 BCC patients with multiple or single BCC	Gene & Polymorphism: GSTP1 BC polymorphism GSTP1 Val105/Val105 combined with CCND1 A polymorphisms	Positively associated with BCC numbers in multiple BCC patients (p=0.03) Positively associated with BCC numbers in multiple BCC patients (p=0.001) and increased risk for multiple BCC (p=0.006)	3	2	To detect patients in higher risk for second primary tumor development after treatment with curative intent	

(Continued)

TABLE 54-2—“Which Patients are More Likely to Develop Second Primary Nonmelanoma Skin Cancer (NMSC)?” Predictors for Multiple Tumor Development in Nonmelanoma Skin Cancer Patients (Continued)

Citation	Design	Patients	Predictors	Efficacy	NOS Scale	Outcome	Clinical importance
(Hajeer et al., 2000)	Case-control study	133 patients each having 2 to 30 BCC and 202 controls	Gene & Polymorphism: TNF a2-b4-d5 haplotype TNF—308 GG polymorphism TNF a1- and a7-containing genotypes within the cases, TNF alleles d4, d6 and haplotype a2-b4-d5	OR=1.98, 95% CI: 1.20-3.26, p=0.007 OR=1.42, 95% CI: 1.03-1.97, p=0.032 Increased in BCC patients (p=0.0271, p=0.0393 respectively) Positively associated with BCC numbers in multiple BCC patients (p=0.023, p=0.006, p=0.007 respectively)	2 2 2	2 2 2	

OR=odds ratio; RR=relative risk; TNF=tumor necrosis factor; GSTP1=glutathione S-transferase p-1; CCND1=cyclin D1.

Graells J (2004). The risk and risk factors of a second non-melanoma skin cancer: a study in a Mediterranean population. *J Eur Acad Dermatol Venereol*. 18:142-147.
Hajeer AH, Lear JT, Ollier WE, et al. (2000). Preliminary evidence of an association of tumour necrosis factor microsatellites with increased risk of multiple basal cell carcinomas. *Br J Dermato* 142:441-5.

Marcelli & Stern RS (2000). Risk of developing a subsequent nonmelanoma skin cancer: a critical review of the literature and meta-analysis. *Arch Dermatol*. 136:1524-1530.

Ramachandran S, Hoban PR, Ichii-Jones F, et al. (2000). Glutathione S-transferase GSTP1 and cyclin D1 genotypes: association with numbers of basal cell carcinomas in a patient subgroup at high-risk of multiple tumours. *Pharmacogenetics* 10:545-56.
Ramachandran S, Rajaratnam R, Smith AG, Lear JT & Strange RC (2009). Patients with both basal and squamous cell carcinomas are at a lower risk of further basal cell carcinomas than patients with only a basal cell carcinoma. *J Am Acad Dermatol* 61:247-51.

Is UV Exposure the Only Significant Risk Factor for NMSC Development? Are there Any Genetic Factors that Predispose to NMSC Development? (Factors Related to Genomic Instability in NMSC)

Cell Cycle – Growth Self Sufficiency

The mouse double minute two homolog (MDM2 gene, locus 12q14.3-q15) oncoprotein promotes cell survival and cell cycle progression by inhibiting the p53 tumor suppressor protein. Recent results suggest that the MDM2 SNP 309 polymorphism alone affects neither the risk nor the age at onset of NMSC. Thyroid autoantigen 70-KD G22P 1 (Ku70 gene, locus 22q11-q13) and x-ray repair complementing defective in Chinese hamster 5 (Ku80 gene, locus 2q35, also known as XRCC5) protein levels were found to be significantly increased in BCC as compared tonormal skin. A direct correlation was found between Ku70 and Ku80 protein levels and expression of the proliferation markers Ki-67/MIB-1 (locus 10q2 5-pter) in basal cell carcinoma. DNA-binding activity was increased in BCC tumor samples as compared to matched control skin samples that were histopathologically negative for cancer.² The percentages of expression for Ki-67, CD31 and epidermal growth factor receptor (EGFR) were significantly higher in the recurrent tumors than in the nonrecurrent ones (Table 54-3). Expression of Ki-67 and CD31 was 271.57 +/- 17.91 and 58.1 +/- 9.37 for the recurrent group and 187.08 +/- 21.48 and 23.9 +/- 5.45 for nonrecurrent group respectively (Table 54-3). Expression of epidermal growth factor receptor (EGFR gene, locus 7p12.3-p12.1) was reported to be positive in basal cell carcinoma cells.⁶¹ Other studies found that the interaction term, glutathione s-transferase p-1 (GSTP1, locus 11q13) Val105/Val105 with cyclin D1 (CCND1, locus 11q13) AA, was associated with tumor numbers in total and multiple concurrent tumors but not with single tumors in BCC patients (see Table 54-2).⁶² In a stepwise model including GSTP1 Val105/Val105, CCND1 AA and their interaction terms as well as GSTM1, GSTT1 and CYP2D6 genotypes, skin type 1 and gender, the combination of genotypes was the best predictor of BCC numbers in patients with multiple BCC (Table 54-2).⁶² Increased expression of the oncogene ERBB3 encoding the tyrosine kinase-type cell surface receptor HER3 (HER3, locus 12q13) was associated with hyperproliferative tumor stages and HER3 expression was suggested to reflect an increased malignant potential in cutaneous lesions.²

Insensitivity to Anti-Growth Signals

Basal cell carcinomas were essentially a molecular 'black box' until some 12 years ago, when identification of a genetic flaw in a rare subset of patients who have a great propensity to develop basal cell carcinomas pointed to

aberrant Hedgehog signalling. Over-expression of sonic hedgehog (SHH, locus 7q36) gene in transgenic human skin (in mice) was reported to induce features of BCC. Furthermore, SHH-activating mutations have also been described in sporadic BCC. High-IR tumors harboured more p53 (locus 17p13.1) and patched drosophila homolog 1 (PTCH, locus 9q22.3) abnormalities compared to low-IR tumors. Therefore, alteration of both genes is likely to play a role in radiation-induced basal cell carcinogenesis. PTCH is the human homologue of the Drosophila-patched (ptc) gene encoding Ptc protein which is a receptor for the diffusible morphogen hedgehog (SHH). Ptc negatively regulates SHH signaling through inhibition of a transmembrane protein Smoothened (Smo). The SHH signaling pathway is highly conserved in different species including humans, where it is involved in determining cell fate and organogenesis.² The WNT genes are a family of highly conserved developmental control genes which encode secreted glycoproteins that are involved in short-range signaling during embryonic patterning. Responses to oncogenic SHH signaling in skin are dependent on canonical Wnt/beta3-catenin signaling, which might be a potential pharmacologic target for BCC.⁶³

Nevoid basal cell carcinoma syndrome (NBCCS) is linked to chromosome 9q22, which harbours the PTCH gene where inactivating germline mutations have been found in BCC tissue. Somatic PTCH mutations have also been described in sporadic BCC. In accordance with a tumor suppressor mechanism for PTCH, loss of the wild-type allele has been demonstrated in BCC from both NBCCS patients and patients with sporadic tumors. Deletions at the PTCH locus were more frequent in tumors with high irradiation exposure. A recent case control study provided indications that azathioprine exposure may be associated with PTCH mutations in post-transplant patients. This might be particularly true in tumors from non-sun-exposed skin.⁶⁴ Dysregulation of the PTCH pathway is thought to be a critical event in BCC development.²

It is believed that cyclins form complexes that phosphorylate retinoblastoma protein (Rb), promoting cell-cycle progression. Rb appears to be the S-phase entrance molecular gate keeper which normally blocks progression and is inactivated via phosphorylation.¹³ The cyclin dependent kinase N2A gene (CDKN2A, locus 9p21) encoding p16 protein may play a role in the pathogenesis of human skin BCC in view of increased p16 mRNA and expressed protein within tumor cells.⁶⁵

Avoidance of Apoptosis/Defective Apoptosis

The tumor suppressor gene (TSG) p53, involved in genome surveillance through the regulation of cell proliferation and death, is frequently inactivated in NMSC, with up to 70% of tumors displaying mutations in the conserved region of one p53 allele. Hitherto, p53-deletion frequencies demonstrated no IR-dose associations. A very common

TABLE 54-3—“Which of Those Patients Treated for Nonmelanoma Skin Cancer (NMSC) Are More Likely to Experience a Recurrence?” Predictors for Recurrence of NMSC

Citation	Design	Patients	Predictors	Efficacy	Outcome Comparability	NOS Scale	Clinical importance
(Brantsch et al., 2008)	RCT	653 white patients Local-recurrence-free survival for SCC	Tumour thickness Desmoplastic growth	SCC: HR=6.03, 95% CI: 2.71–13.43, p<0.0001 HR=16.11, 95% CI: 6.57–39.49, p<0.0001			
(Mullen et al., 2006)	Retrospective cohort study	653 white patients Metastasis-free survival for SCC	Tumour thickness Tumour horizontal size Tumour site (Ear, ligt not Ear) Immunosuppression	HR=4.79, 95% CI: 2.22–10.36, p=0.0001 HR=2.22, 95% CI: 1.18–4.15, p=0.0128 HR=3.61, 95% CI: 1.51–8.67, p=0.0040 HRT=4.32, 95% CI: 1.62–11.52, p=0.0035		1 2 2	

(Janisson-Dargaud et al., 2008)	Case-control study	20 patients who had subsequent local recurrences and 20 matched controls without recurrences	Aneuploidy		2	1	2
(Cheretis et al., 2008)	Case-control study	52 primary BCCs which recurred and of 52 cases of BCC which did not recur	Nuclear morphometry z-value max gray level z-value gray level variance	BCC: p=0.022 p=0.011	2	2	2
(Yerebakan et al., 2003)	Dependent samples	26 basal cell carcinoma cases, 14 of whom had a recurrence after an average of 3.7 years, and 12 of whom had no recurrence during an average of 4.4 years follow-up	Ki-67 and CD31	Non Recurrent 271.57 +/- 17.91 58.1 +/- 9.37	2	2	1
(Boztepe et al., 2004)	Observational cohort study	261 BCC tumours	Primary BCC Recurrent BCC	p 187.08 +/- 21.48 23.9 +/- 5.45 3.3% 5-year recurrence rates 7.3% 5-year recurrence rates			
				To detect patients in higher risk for recurrence after treatment with curative intent			
				To detect patients in higher risk for recurrence after treatment with curative intent			
				To detect patients in higher risk for recurrence after treatment with curative intent			

z-value gray level=a qualitative marker of nuclear morphometry introduced by the authors(Cheretis et al., 2008)
 Boztepe G, Hohenleutner S, Landthaler M & Hohenleutner U (2004). Munich method of micrographic surgery for basal cell carcinomas: 5-year recurrence rates with life-table analysis. *Acta Derm Venereol.* 84: 218–222.

Brantsch KD, Meissner C, Schonfisch B et al. (2008). Analysis of risk factors determining prognosis of cutaneous squamous-cell carcinoma: a prospective study. *Lancet Oncol.* 9:713–20.
 Cheretis C, Angelidou E, Dietrich F, Politis E, Kiaris H & Koutsilini H (2008). Prognostic value of computer-assisted morphological and morphometrical analysis for detecting the recurrence tendency of basal cell carcinoma. *Med Sci Monit.* 14: MT13–9.

Janisson-Dargaud D, Durlach A, Lorenzato M, Grange F, Bernard P & Birembaut P (2008). Aneuploidy, but not Ki-67 or EGFR expression, is associated with recurrences in basal cell carcinoma. *J Cutan Pathol.*
 Mullen JT, Feng L, Xing Y, et al. (2006). Invasive squamous cell carcinoma of the skin: defining a high-risk group. *Ann Surg Oncol.* 13:902–9.
 Yerebakan O, Ciftcioglu MA, Akkaya BK & Yilmaz E (2003). Prognostic value of Ki-67, CD31 and epidermal growth factor receptor expression in basal cell carcinoma. *J Dermatol.* 30:33–41.

polymorphism of p53 is that of codon 72, which codes either for a proline (P72) or an arginine (R72). The two alleles differ in their biologic properties: P72 is a stronger inducer of p21, while R72 induces 5–10 times more apoptosis. It is not known, however, whether this polymorphism influences genomic stability.² The influence of p53 codon 72 polymorphism on cancer risk has been studied for different types of cancer with mixed and inconsistent results.¹³ No significant association was reported between p53 genotype and BCC. The germline Arg72Pro polymorphism alters the protein's biochemical functions, and may confer individual susceptibility to skin cancer. Compared to the Arg/Arg genotype, the Pro/Pro genotype was reported to be associated with BCC risk, while no association was observed between the polymorphism and SCC risk⁴⁴ (see Table 54-1). It has been suggested that p53 mutation is a crucial but late event in BCC progression, an event also pertinent for other cancers.¹³ Therefore, p53 mutations could only be biomarkers of limited value.

Several p53 codon mutations have been linked to nonmelanoma skin cancer (particularly SCC) development in renal transplant patients.³⁷ The same study reported no differences in p53 codon 72 polymorphisms and XPD gene polymorphisms between renal transplant patients with skin tumors and control individuals of the same Northern European Caucasian population.³⁷ Other authors did not find any significant association either between p53 polymorphism, that of codon 72, codes either for a proline (P72) or an arginine (R72) and basal cell carcinoma (BCC), squamous cell carcinoma (SCC), or both combined.⁶⁶

An interesting observation concerns the oncogene B-cell leukemia 2 (Bcl-2, locus 18q21.3) protein expression; Bcl-2 was found to be expressed in BCC but not in SCC. The authors concluded that Bcl-2 overexpression in BCC supports the observation that these tumor cells are derived from basal keratinocytes. On the contrary, in SCC, lack of Bcl-2 expression indicates that origin of tumor cells could be from more differentiated suprabasal keratinocytes.⁶⁷

The Family with sequence similarity 82, Member A2; (FAM82A2, locus 15q15.1, also known as protein tyrosine phosphatase-interacting protein 51: PTPIP51 Family with sequence similarity 82, Member C and FAM82C) is thought to be involved in a mitochondria/cytochrome c-mediated apoptosis pathway. The FAM82A2 protein was reported to be overexpressed in both BCC and SCC tumors. FAM82A2 was also detected in the peritumoral tissue,⁶⁸ thus the protein may play a crucial role in keratinocyte proliferation and escape from apoptotic signaling.

Limitless Replicative Potential of Cells

Increased DNA content is a basic feature in cancer cells, allowing for more mutations and greater genomic instability. Aneuploidy indicates widespread DNA changes as a result of genomic instability. It is known that the assessment of the DNA content of cells can be accomplished with

the use of a flow cytometer technique.¹³ Nuclear morphometry is an alternative method of quantitatively evaluating nuclear DNA content. With regard to BCC, nuclear morphometry could not distinguish between primary and recurring tumors.² Cheretis et al.⁶⁹ in a recent publication argue that nuclear morphometry when evaluated through computer-assisted algorithms, may be a useful adjunct to histopathologic and demographic markers in order to detect which BCC tumors are going to recur. A case control study reported presence of aneuploidy in 78% of primary BCC in patients who experienced recurrences compared to only 32% of primary BCC in the control group.⁷⁰ The authors concluded that aneuploidy is a risk factor for recurrences, which should be useful in clinical practice (see Table 54-3).

Sustain Angiogenesis

In BCC tumors, vascular endothelial growth factor (VEGF, locus 6p.12) was expressed by tumor epithelial cells, predominantly at the invasive tumor front and its expression was significantly greater than in adjacent skin. More widespread VEGF expression was found in cases of SCC, and it was significantly associated with the degree of tumor differentiation.⁷¹

BCCs with high chemokine, CXC motif, receptor 4 (CXCR4, locus 2q21) expression had concomitantly higher micro-vessel density, as compared with those with low CXCR4 expression. Chu et al. found that Chemokine, CXC motif, ligand 12 (CXCL12, locus 10q11.1, also known as stromal cell-derived factor-1, SDF-1) induced angiogenic activity in human BCC cells, both *in vitro* and *in vivo*. CXCL12 significantly upregulated several angiogenesis-associated genes such as interferon-alpha-inducible protein 27, interleukin (IL)-6, bone morphogenetic protein (BMP)-6, suppressor of cytokine signaling 2 (SOCS2) and cyclo-oxygenase 2 (COX)-2 in human BCC cells. Among them, IL-6 was the earliest and highest up-regulated gene whose induction was observed within 6 hours of the commencement of CXCL12–CXCR4 interaction.⁷² Despite the fact that BCC is not widely regarded as a tumor with high vascularity (cause for that is the necrosis/ulceration in the center of the tumor) it appears that BCC tumor cells exhibit alterations in angiogenesis signaling. Further research is warranted in this field.

Invade and Proliferate

Cadherins are cell adhesion molecules thought to play a vital role in cell–cell adhesion. Loss or down-regulation of their expression has been implicated in neoplasia. In gastrointestinal cancers, a significant reduction in cadherin expression has been documented as the dysplasia to adenocarcinoma sequence progresses.¹³ Similarly, few existing studies demonstrated that normal skin and skin showing mild and moderate solar elastosis strongly

expressed membranous E-cadherin and beta-catenin. E-cadherin expression was progressively reduced in the epidermis of skin with severe solar elastosis through solar keratosis to SCC. The same phenomenon was observed for beta-catenin starting from solar keratosis.⁷³ Suppression of E-cadherin expression and loss of its function fundamentally modified squamous cell carcinoma progression by activating a highly invasive, aggressive tumor phenotype, whereas maintenance of E-cadherin prevented invasion and limited tumor progression in vitro.⁷⁴

Basal Cell Carcinoma, Susceptibility to [Number], BCC [Number] Gene Family

The primary environmental risk factor for BCC is sun exposure, but genetics also has a substantial role. Some of the sequence variants that confer susceptibility seem to operate through their association with fair-pigmentation traits (common among Europeans), resulting in reduced protection from the damaging effects of ultraviolet (UV) radiation as described in section 4.8.1.3. Other sequence variants have no obvious role in pigmentation or UV susceptibility but instead seem to operate in the contexts of tumor growth and differentiation of the basal layers of the skin, as earlier described in section 4.8.1.4. During 2009, specific loci in the human genome have been renamed to exhibit their association with BCC development. Susceptibility to basal cell carcinoma is now considered a genetically heterogeneous trait. Loci associated with susceptibility have been identified on chromosomes 1p36 (BCC1), 1q42 (BCC2), 5p15 (BCC3), 12q13 (BCC4), 9p21 (BCC5), and 7q32 (BCC6) (see Table 54-1).

Which Patients Are More Likely to Develop Second Primary NonMelanoma Skin Cancer?

The risk of developing a subsequent nonmelanoma skin cancer in people who have developed a first nonmelanoma skin cancer is not well defined.³⁴ Marcil et al. in their meta-analysis concluded that the 3-year cumulative risk was 44% (increased) for BCC after an index BCC, 18% (increased) for SCC after an index SCC, 6% (reduced) for SCC after an index BCC, and 47.25% for a nonmelanoma skin cancer after an index nonmelanoma skin cancer.⁷⁵

Other authors reported that up to 39% of patients initially referred with BCC either presented with multiple primary lesions or experienced a subsequent tumor within 2 years. Multivariate analysis models showed older age, multiple tumors, and male sex as significant prognostic factors for second primary NMSC.⁷⁶ (see Table 54-2). A statistically significant decrease in size of the second primary NMSC when it was compared to the first primary NMSC has also been reported. The authors did not comment on whether the latter was an effect of closer surveillance.² History of

previous NMSC was reported to confer increased risk for second tumor development compared to the overall population, in a study which included over 4,000 NMSC patients⁷⁷ (Table 54-2). Some aforementioned single nucleotide polymorphisms (SNPs) or their combinations (haplotypes) have been associated with increased or reduced risk for second primary NMSC development (Table 54-2). Another study reported that patients with history of both BCC and SCC were less likely to develop a further BCC during the 5 years after initial presentation when compared to the group of patients with history of BCC only.⁷⁸

Tumor Site

Some authors reported higher risk for second primary BCC in certain tumor locations. Patients with truncal BCC were reported to have augmented predisposition to multiple tumors. Other authors did not find any relation between tumor site and second primary. Anatomic distribution of BCC is consistent with general levels of sun exposure across body sites,² thus site selectiveness is probably confounded by photoaging. On the other hand, the proportion of patients with truncal BCC could have genetic risk factors that predispose to BCC development.

Which of Those Patients Treated for NMSC are More Likely to Experience a Recurrence?

BCC Recurrence

The 5-year recurrence rates were reported to be 3.3% for primary and 7.3% for recurrent basal cell carcinomas (Table 54-3).⁷⁹ The use of different statistical methods to report the recurrence rates mainly accounts for the discrepancy among the various studies. Some authors suggested that life-table analysis provides the best approximation of the true recurrence rates.⁷⁹ Histologic markers for recurrence do not exist to date. Of note, margin involvement could be related to peripheral healthy tissue sacrifice.² Nuclear morphometry and few aforementioned biomarkers could have some value to predict risk for BCC recurrence (Table 54-3).

SCC Recurrence

In contrast to BCC, SCC has the potential to metastasize and thus disease recurrence cannot be confined to local recurrence alone but also concerns regional recurrence or even metastasis. Last year, an RCT⁵ reported specific risk factors, which were associated with SCC tumor recurrence, namely tumor thickness in mm and presence of desmoplastic growth (Table 54-3). A retrospective cohort study reported scar carcinoma, history of burn in the tumor site, presence of chronic sinus tract/ulcer, tumor size >2 cm, nodal disease, poorly differentiated versus moderately

and well differentiated and well differentiated versus moderately and poorly differentiated as significant risk factors to predict local, regional, or metastatic recurrence (Table 54-3).⁸⁰

Are There Patients in Higher Risk for Nonmelanoma Skin Cancer Metastasis?

Histologic diagnosis (differentiation, tumor thickness, depth of invasion, perineural involvement), size (horizontal dimension/diameter) and immune status of the patients all have a role in predicting the risk of metastasis.⁶ However, no specific relative risks have been attributed to the majority of these risk factors by appropriately conducted clinical trials.

In the RCT by Brantsch et al.⁵ tumor thickness, tumor horizontal size, immunosuppression, and tumor location in the ear were reported as statistically significant risk factors for metastasis of SCC (Table 54-3). Of note, tumor thickness and size are the main variables measured by the widely applied TNM staging system. Tumor location in the ear and genitalia have long been associated with increased risk for SCC metastasis.

A retrospective cohort study concluded that locally advanced tumors are at risk of lymph node metastasis. Increased risk was associated to previous lesions at tumor site. TNM stage, T4 classified tumors have worse prognosis.⁸¹ Of note in the latter study lymph node recurrences in N0 patients, once treated, did not affect survival. The authors reported that their results did not support indication for elective lymphadenectomy or sentinel node mapping.⁸¹

Does BCC Metastasize? Are There Patients in Higher Risk for BCC Metastasis?

NMSC Progenitor Stem Cells

A previously published hypothesis argues that there is a relationship between BCCs and the cells of the stem cells of the hair follicle. The results of a case control study showed that neural cell adhesion molecule (NCAM) immunoreactivity was present in 31 of 34 patients with BCCs, but not in patients with SCC or controls. This pattern corresponds to the expression patterns of the outer hair root sheath of the vellus hair follicle.⁸² Similar to embryonic hair follicles, human BCC cells showed increased levels of cytoplasmic and nuclear beta-catenin and expressed early hair follicle lineage markers.⁶³ Another case-control study concluded that BCC tumor cells likely originate from the more mature nestin-negative/K15-positive/CD34-negative outer-root sheath cells, while SCC cells likely originate from the nestin-negative/K15-positive/CD34-negative keratinocytes of the basal cell layer in the epidermis.⁸³

Monoclonal Origin

It was argued that distinct BCC arising in the same patients could be of monoclonal origin. The authors supported their hypothesis via X-inactivation and loss of heterozygosity (LOH) studies at the 9q22.3 region. However, currently available evidence does not support the argument that BCC metastasizes. No well-designed studies have documented BCC tumors to discontinuously spread to anatomically distinct body sites far beyond their point of origin. Limited existing case reports could be subject to second primary development bias.²

Methods

We systematically searched the literature for studies assessing the incidence, the probability of recurrence and/or second primary tumor development, the genetic basis of host response to UV DNA damage, the effect of UV on generation of reactive oxygen species (ROS) and their detoxification, UV-induced skin immunity modifications, and the role of genomic instability with focus on the potential use of these biomarkers to the treatment and prognosis of NMSC patients.

The following databases were electronically searched to identify eligible studies to be included in this chapter.

- Cochrane Database of Systematic Reviews to September 2009
- Cochrane Central Register of Controlled Trials (Clinical Trials)
- MEDLINE from 1950 to September 2009.
- OMIM to October 2009.
- EMBASE from 1980 to September 2009.

The search strategy included any of the following medical subject headings (MeSH) and/or terms: “skin”, “skin neoplasms”, “acanthoma”, “SCC”, “Carcinoma, Squamous Cell”, “Neoplasms, Squamous Cell”, “epithelioma”, “Skin Diseases, Viral”, “Skin Diseases, Papulosquamous”, “BCC”, “basal cell carcinoma”, “basal cell cancer”, “neoplasms, basal cell”, “nodular BCC”, “nevroid BCC”, “basal cell nevus syndrome”, “Gorlin syndrome”, “rodent ulcer”, “basal cell epithelioma”, “basalioma”, and “nonmelanoma skin cancer”.

These terms then were combined with the MeSH terms “epidemiology,” “histology,” “second primary,” “multiple tumor”, “recurrence”, “Neoplasm Metastasis”, “tumor site”, “risk factor,” “clinical”, “demographic” and “gene”, “DNA Repair”, “DNA Repair Enzymes”, “DNA Repair-Deficiency Disorders”, “Risk Factors”, “Genomic Instability”.

The search strategy used to locate randomized controlled trials (RCTs) included search terms 1–29 as given in the Cochrane Reviewers’ Handbook⁸⁴, Appendix 5b.2. Since the search strategy with the relevant search terms was expected to result in an inadequate number of RCTs, we also included nonrandomized studies. For studies identified that are of nonrandomized design, case-control and

cohort studies, the quality of these was assessed using an appropriately modified version of the Newcastle-Ottawa Scale (NOS),⁸⁵ whereby the selection of the cases and controls, the comparability and exposure was assessed.

Articles were excluded if they were case reports or reviews, if the article focused only on treatment or diagnosis, or if the article did not reference NMSC cases. Articles published in languages other than English were evaluated from their English abstract when available. Data about patient age, sex, tumors, risk factors, and potential follow-up were abstracted. To be eligible, a published study must have explicitly stated the probability of developing a certain outcome under the influence of one or more risk factors. Only studies conferring statistically significant results were selected for tabular presentation.

The initial Medline search strategy resulted in 78,326 articles that included the “skin neoplasms” term. This number was reduced to 56,826 when the Mesh term “melanoma” was inserted preceded by “NOT” option. When the remainder terms were used, a total of 528 articles were collected. The article abstracts were reviewed, and 108 articles, which matched the search intent criteria, were obtained for review. An additional 11 articles were identified within the citations of articles reviewed.

For studies, which reported on chromosomal locations and gene names, the information was inputted in the OMIM database and OMIM nomenclature was obtained for use in this chapter.

CONCLUSIONS AND FUTURE PERSPECTIVE

Socioeconomic Burden of the Disease and Risk Factor Utility

While the incidence of nonmelanoma skin cancer increases in both the United States and Europe, limited data exist about the financial burden generated by the disease. Studies from Canada⁸⁶ and the United States⁸⁷ reported the cost of treating a single primary nonmelanoma skin cancer to range from US\$ 471 up to \$ 3,460, depending on the treatment modality of choice. Nonmelanoma skin cancer was reported to rank fifth among all cancers when annual mean Medicare payment was examined. More specifically, nonmelanoma skin cancer followed lung, prostate, colon, and breast cancer and preceded leukemia, non-Hodgkin’s lymphoma, ovarian, pancreatic, stomach cancers and melanoma.⁸⁸ The authors proposed that in addition to classifying cancers by number of cases and number of deaths, the financial impact of treatment could also be used to prioritize different malignancies. Such a scheme would rank nonmelanoma skin cancer far higher than would death statistics. In light of its already high and rising incidence, the cost of nonmelanoma skin cancer care to Medicare is likely to increase.

Apart from the burden generated for the treatment of the disease, those that are diseased suffer further

socioeconomic consequences, mainly being less concerned about their general health, feel shame about their appearance, and losing time from work or caring for others.⁹¹

The estimated increase of the socioeconomic consequences of NMSC might be attenuated should preventive strategies be applied to high risk populations. Deployment of risk factors is essential to characterize high risk populations. Deployment of currently available biomarkers to facilitate earlier diagnosis in high-risk patients is anticipated to reduce treatment costs too. To maintain the cost-effective management of nonmelanoma skin cancer, the current low per-patient cost of its management should be maintained. In this regard, treatment modalities like simple surgical excision, Mohs micrographic surgery, irradiation therapy and imiquimod chemotherapy, need to be evaluated with regard to their risk for recurrence. A recent randomized clinical trial concluded that Mohs micrographic surgery is more efficient for the treatment of recurrent BCC when compared to surgical excision. When, primary BCC was concerned, the same study concluded that both treatment modalities were similarly efficient but surgical excision was less costly.⁸⁹ Another randomized clinical trial comparing MMS to surgical excision is currently recruiting participants in Europe (NCT00699829). Surgery and radiotherapy appear to be the most effective treatments, the best results being obtained with surgery.⁹⁰ Topical imiquimod could become a useful treatment for superficial and low-risk BCCs and would allow dermatologists to concentrate on the high-risk BCCs, but long-term results comparing topical imiquimod with excisional surgery are still required.⁹⁰ Vigilant selections of patients to be treated with each modality, based on evidence-based risk factors is a requisite.

Risk Factors for NMSC: Future Perspective

To facilitate earlier diagnosis, a currently recruiting study is held at the University of Texas, MD Anderson Cancer Center, in which a spectral diagnosis probe is used to detect cutaneous malignancies (NCT00476905).

Since patients with Basal Nevus Syndrome (NBCCS) and kidney transplant recipients are at higher risk of developing new BCC tumors, new trials for the prevention of BCC have logically focused on them. Celecoxib versus placebo twice daily for 2 years has been supplemented to a subset of patients (NCT00023621). The results of the study are pending. In patients with NBCCS, the efficacy and safety of a systemic hedgehog pathway antagonist (GDC-0449) are studied in an ongoing trial (NCT00957229). Another study stratifies patients with high risk for BCC according to disease type (xeroderma pigmentosum vs nevoid basal cell carcinoma syndrome) and tests the effectiveness of isotretinoin in preventing or slowing the growth of skin cancer (NCT00025012).

In kidney transplant recipients, an ongoing clinical trial (NCT00089180) studies T4N5 liposomal lotions ability in

preventing the recurrence of nonmelanoma skin cancer. The use of acitretin versus placebo in preventing skin cancers in patients with previously treated skin cancers who have undergone organ transplantation is under study (NCT00003611). Another possible preventive treatment is that of PDT With Metvix® 160 mg/g cream which is studied in organ transplant recipients with nonmelanoma skin cancer (NCT00472459). Results are pending.

A randomized phase II trial to study the effectiveness of a low-fat, balanced diet to prevent disease progression in patients with nonmelanoma skin cancer is also ongoing. (NCT00003097) Acitretin (NCT00644384) and eflornithine (NCT00005884) are two new agents under trial for the prevention of nonmelanoma skin cancer. Ongoing RCTs aim to determine the chemopreventive efficacy in patients at high risk for nonmelanoma skin cancer, or patients who have previously received treatment for nonmelanoma skin cancer. NCT00847912 is a clinical trial aimed to examine if 5-fluorouracil (5-FU) skin cream can prevent the growth of new skin cancers on the face and ears. The cost of trying to prevent skin cancer will be compared to the usual cost of treating skin cancer. Patients who have been treated for two or more skin cancers within the past 5 years are being enrolled.

While there are some randomized clinical trials on prevention of nonmelanoma skin cancer, most of them are targeted at preventive regimens rather than risk factors. This is commonsensical, keeping in mind that the expenditure of an RCT is large and funds are mainly drawn from the drug industry.⁹² It is not unusual for such studies to be prematurely terminated; as a study to determine the efficacy of topical tretinoin cream for the prevention of nonmelanoma skin cancer was terminated 6 months early because of an excessive number of deaths in the tretinoin-treated group. (NCT00007631).⁹³ Importantly, no study to date reports the cost-effectiveness or preventive strategies to reduce the economic burden of nonmelanoma skin cancer. Since a key role of clinical trials is to improve efficiency and reduce health costs,⁹² one could anticipate that new clinical trials would be designed to evaluate the prognostic significance of a number of risk factors.

Pharmacogenomics is the branch of pharmacology which deals with the influence of genetic variation on drug response in patients, by correlating gene expression or single-nucleotide polymorphisms with a drug's efficacy or toxicity. Pharmacogenomics aims to develop rational means to optimize drug therapy, with respect to the patients' genotype, thus to ensure maximum efficacy with minimal adverse effects. Such approaches promise the advent of "personalized medicine"; in which drugs and drug combinations are optimized for each individual's unique genetic makeup. The VDR gene is such an example when SCC tumors are concerned. Vitamin D supplementation maybe inexpensive, but RCTs reported no benefit for the general population.

Despite spending much time and effort for developing biomarkers, to date no biomarker could be of use in identifying which patients are going to develop a second primary nonmelanoma skin cancer or which treated nonmelanoma skin cancer tumors are going to recur; such information would be of importance for reducing follow-up and treatment cost. On the other hand, conventional clinical and demographic prognostic factors for nonmelanoma skin cancer have long been reported (Tables 54-2 and 54-3). Clearly, exposure to UVR is an important initiating factor in skin cancer, although the exact connection between nonmelanoma skin cancer risk and nature, extent, and timing of exposure, remains poorly understood. Excluding PCTH mutations, data so far suggest that risk of NMSC is likely to result from the combined effect of many genes, each with a relatively weak individual contribution. Presumably, the effect of genomic instability results in dysregulation of expression of key TSG or oncogenes. Whether these alterations could be of prognostic value for the clinical practice is not clear to date. Certain genomic alterations have been associated with increased or reduced risk for NMSC (Table 54-1), with a second primary NMSC (Table 54-2) or with a recurrent tumor (Table 54-3). However, use of these biomarkers in everyday practice should be supported by further studies, mainly for its cost-effectiveness. Such studies also add to the currently available knowledge regarding NMSC aetiopathogenesis providing further justification for their expenditure.

Several SNPs predisposing to NMSC development have been described previously in the manuscript. Basic medical research is expected to contribute a large number of associations between risk for NMSC development and various genes. In the future, microarray analyses of a person's DNA sequences may be the most cost-effective way to predict risk for NMSC development. Evidence reviewed herein suggests that there may be more research targeted in BCC when compared to SCC. In this regard, six distinct genes signifying susceptibility to BCC have been named after their risk predicting capacity within 2009; their number is expected to rise. The reason for that may be the longer life expectancy of BCC patients, the greater cumulative incidence of the disease, and the more homogenic differentiating profile of BCC cancer cells when compared to SCC cancer cells. While for BCC development the genetic hallmark is abrogation of the PTCH-sonic hedgehog pathway, little is known about the causal alterations of SCCs. However, the complexity of the genetic alterations (numerical and structural aberration profiles) in SCCs argues for several levels of genomic instability involved in the generation and progression of skin cancer.

CONCLUSIONS

Given the continuously rising life expectancies of new born children⁹⁴ and the previously reported role of skinaging in nonmelanoma skin cancer development, it is anticipated that the number of patients who experience

a nonmelanoma skin cancer will also rise. The incidence of nonmelanoma skin cancer is increasing year by year and the number of immunocompromised patients who exhibit a higher risk is on the increase.³⁴ Furthermore, the usually reported patient incidence rates of BCC and SCC substantially underestimate the burden of nonmelanoma skin cancer in the population when compared to tumor-incidence rates.⁹⁵ A study in US Veteran's concluded that nonmelanoma skin cancer is being diagnosed at a younger age and more commonly on the extremities than in the past.⁹⁶ Thus, more research targeted on nonmelanoma skin cancer is justified. New approaches in early identification of nodal metastases, treatment, and prevention of local recurrences, and second primary malignancies are warranted.

Existing demographic and clinical risk predictors for nonmelanoma skin cancer derived from open uncontrolled studies which are mainly unmatched and retrospective.

Not enough information exists on the possible value of these factors regarding the characterization of high risk populations (see Table 54-1). Furthermore, the predictive value of available biomarkers in the development of second primary or recurrent tumors is also uncertain (Tables 54-2, 54-3). Limited existing data presented in this chapter suggest that demographic and clinical risk factors are of the same or more likely higher predictive value when compared to biomarkers. Moreover, they are indisputably cheaper and easier to monitor even in developing countries.

Conclusively, it is suggested that further studies aimed in nonmelanoma skin cancer are needed to present better evidence about the predictive value of certain demographic, clinical, and histologic factors in identifying high-risk populations. The authors of this chapter have conducted a study of this type. Studies have now been published. Should the Editor wish to add them to chapter references.^{97,98}

What We Know

- A number of clinico-epidemiologic factors are associated with higher risk for nonmelanoma skin cancer development.
- Patients with prolonged Ultra Violet (UV) radiation exposure are at higher risk of developing nonmelanoma skin cancer. The association between risk and UV exposure appears to be less dose-responsive in BCC than in SCC.
- Biomarkers for NMSC can be classified as:
 - Biomarkers related to defective host response to ultraviolet radiation
 - Biomarkers related to Genomic instability
- A subset of patients with NMSC exhibits a higher risk of developing a second primary NMSC. Another subset of patients with NMSC exhibits a higher risk of experiencing a recurrence. These patients may be screened via certain risk factors and followed up in a structured fashion.
- BCC is believed to originate from stem cells of the hair follicle. SCC is believed to originate from stem cells of the basal cell layer in the epidermis.
- BCC does not metastasize.
- The incidence of NMSC is anticipated to rise as well as the socioeconomic burden of the disease.
- Research on biomarkers for NMSC is justified in order to develop preventive and follow-up strategies and to better understand the pathophysiologic process of the disease so as to facilitate more efficient treatment modalities.
- Conventional clinical and demographic risk factors need also to be studied more thoroughly since they can be most cost-effective for the prevention of the disease.
- Further research on vitamin D receptor polymorphisms could allow for separation of the group of patients for whom vitamin D supplementation shall have a protective effect against NMSC development. On the contrary, higher risk for SCC was reported in women with a specific VDR Bsm1 polymorphism and high vitamin D intake. Pharmacogenomics screening in the general population is already of value to avoid unfavorable effects of Vitamin D supplementation.
- Six distinct loci associated with susceptibility to basal cell carcinoma have been named to date.

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Risk Factors for Alopecia

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INTRODUCTION

The alopecias are a diverse group of disorders characterised by loss of hair. Their causes are similarly diverse involving varying degrees of genetic and environmental influences. In this article, we discuss the risks associated with the development and prognosis of some of the more common types of alopecia including pattern hair loss, alopecia areata, cicatricial alopecia, and chemotherapy alopecia.

PATTERN HAIR LOSS

Pattern hair loss, or common balding, is a familiar human trait that occurs in both men and women (Figure 55-1). The patterns of hair loss in the two sexes generally differ although there is overlap and racial variation. For example, a ‘female’ pattern characterised by a diffuse reduction in hair density with retention of the frontal hair line is occasionally seen in men and a ‘male’ pattern, with



FIGURE 55-1 Female pattern hair loss.

fronto-temporal recession and vertex balding, occasionally occurs in women. In general terms, the etiology of male balding is quite well defined. Less is known of the causes of pattern hair loss in women. The term ‘androgenetic alopecia’ has been used to describe pattern hair loss. The role of androgens and genetic factors is well established in male balding but the etiology in women is less clear-cut, hence the recent preference for using the term ‘female pattern hair loss’ (FPHL).

Risk Factors for Pattern Hair Loss in Men

Male balding is determined by three factors – age, androgens, and a genetic predisposition.

Age

In view of its inevitability, it is difficult to regard aging as a risk factor in male balding. Nevertheless, the frequency and severity of balding increase in the population as a function of age and the risk that an individual will develop balding clearly increases with advancing years. Almost all Caucasian men develop some recession of the frontal hair line at the temples during their teens. Deep frontal recession and/or vertex balding may also start shortly after puberty, although in most men the onset is later. Hair loss progresses to end stage balding (i.e., Norwood-Hamilton stage VI-VII, in 50-60% of men by the age of 70). A small proportion of men (15-20%) do not show balding, apart from post-pubertal temporal recession, even in old age. Some authorities have suggested that scalp hair loss in elderly men may develop independently of androgens (senescent alopecia) but this remains to be verified.¹

Androgens

It has been known since ancient times that eunuchs do not go bald. Hippocrates stated that ‘eunuchs are not subject to gout nor do they become bald’ (Aphorisms VI, 28). The role of testosterone was first recognized by James Hamilton, an American anatomist.² He observed that men castrated

before puberty retained a pre-pubertal hair line and did not go bald. Of twelve such men who were subsequently treated with testosterone, four developed typical male hair loss. Castration later in life halted the progression of hair loss but did not result in regrowth of hair.

Testosterone is the major circulating androgen in men. However, it is the more potent androgen, dihydrotestosterone (DHT), the 5 α -reduced metabolite of testosterone that is responsible for driving hair loss. The conversion of testosterone to DHT is catalyzed by the enzyme 5 α -reductase. There are two isoforms of 5 α -reductase which are encoded by different genes. Males with a mutation in the gene for the Type 2 isoform (pseudovaginal perineoscrotal hypopspadias) have low circulating levels of DHT, ambiguous external genitalia and do not go bald.³ Accordingly, treatment of male balding with finasteride, an inhibitor of type 2 5 α -reductase, prevents progression of balding in most men and stimulates some recovery of hair growth in about two thirds.⁴ This latter finding also illustrates that, contrary to Hamilton's conclusions from his observations in eunuchs, male balding is partially reversible.

Androgens act on tissues via binding to a specific intracellular protein, the androgen receptor, a member of the steroid-thyroid nuclear receptor superfamily. Mutations in the androgen receptor gene are responsible for the androgen insensitivity syndrome. XY individuals with the complete form of the syndrome (Complete Androgen Insensitivity Syndrome), in which there is failure of functional androgen receptor expression, have intra-abdominal testes but female external genitalia and body form, and female psychosexual development. After puberty, circulating testosterone is in the normal or elevated male range but pubic and axillary hair fail to develop, and there is no beard growth and no balding.⁵

A role for androgens in the etiology of male balding is incontrovertible. Nevertheless, other factors are clearly involved as not all men develop balding despite similar androgen levels to those that do. The above discussion emphasizes that there are multiple points in the pathway leading to androgen action in the target tissue that may modulate the response but to date we have little evidence of what these factors might be. There have been several studies reporting higher levels of androgens in balding men compared to men without hair loss. These include elevated DHT: testosterone ratios,^{6,7} raised levels of free testosterone,^{8,9} and dehydroepiandrosterone in plasma.¹⁰ However, all are quite subtle and total testosterone levels and other features of 'masculinity'¹¹ do not differ between balding and nonbalding groups.

Genetics

Twin studies demonstrate that the predisposition to male balding in young men is predominantly caused by genetic factors.^{12,13} Published concordance rates for monozygotic twins are around 80–90%, with consistently lower rates

in dizygotic twins. The most obvious risk factor is paternal hair status and several studies have shown there is a high frequency of balding in the fathers of bald men. For example, Ellis and colleagues reported that 32 of 54 bald men (59.3%) had fathers with a greater degree of baldness, whereas only one of 65 sons of 50 non-bald controls had type III baldness or greater.¹⁴ In a study involving 572 men aged 16–91, there was a significant increase in the risk of balding in young men with a balding father over those with a non-bald father (odds ratio (OR) 5.5, 95% CI 1.26–23.99), which fell with increasing subject age to approach unity in elderly men.¹⁵ The opposite trend was seen in non-bald men where the risk of nonbalding in men with a non-bald father increased with age (OR 3.2, 95% CI 1.82–5.58 in subjects aged 70 and over).

There are also racial differences in the prevalence of male balding, presumably genetically determined, although there are no parallel studies in different racial groups. Compared to Caucasians balding is less common in oriental men. Takashima and colleagues reported the male balding starts approximately one decade later in Japanese men than in Caucasians and the prevalence is about 1.4 times lower in each decade group.¹⁶ In Korean and Chinese men the frequency is 20–40% lower than in Caucasian men in the 40–70 age group, although the difference becomes less pronounced with advancing age.^{17,18}

Androgenetic alopecia is probably a polygenic trait.¹⁹ Three independent candidate gene studies have found significant associations, positive^{20,21} and negative,²² with variant regions of the androgen receptor (AR) gene. Genome wide scans have also identified susceptibility loci at 3q26²³ and 20p11.22.^{24,25} Richards and colleagues calculated that men carrying risk alleles at AR and 20p11.22 had a seven-fold increased risk of androgenetic alopecia.²⁵

Risk Factors for Pattern Hair Loss in Women

Age

As in men, the population frequency and severity of FPHL increase with age. Two studies in Caucasian women in the United Kingdom and United States reported prevalence rates of 3–6% in women aged under 30, increasing to 29–42% in women aged 70 and over.^{26,27} The frequency is lower in oriental women.^{17,18} Cross sectional data show that, from around the age of 30, hair density in the female population declines gradually with advancing years. Mean hair diameter also falls over a similar age range.²⁶ These data show no evidence that the decline in hair density and hair diameter accelerates following the menopause.

Androgens

Several studies have reported that women with hair loss are more likely to have elevated androgen levels or show an increased frequency of other features of androgen excess

than women without hair loss. Futterweit and colleagues studied 109 women with hair loss and reported that 38.5% showed clinical or biochemical evidence of androgen excess.²⁸ In a series of 187 women with hair loss, Vexiau et al. reported abnormal hormonal profiles, mostly of minor degree, in 67% of women with hair loss alone and in 84% of women who were also hirsute.²⁹ In a series of 89 women presenting to a trichology clinic with hair loss 67% showed ultrasound evidence of polycystic ovaries compared to 27% in a control group of 73 women, and 21% were significantly hirsute compared to 4% of controls.³⁰ However, other investigators have failed to find evidence of raised androgen levels in women with FPHL,³¹ and in all studies there is a variable proportion of women with hair loss who do not show clinical or biochemical signs of androgen excess.

There is limited information on the frequency of hair loss in women with hyperandrogenism. Reports of hair loss in women with androgen secreting tumors^{32,33} predated Hamilton's seminal observations on testosterone and male balding. In a small personal study, seven of 21 women referred with hirsutism (33%) also had pattern hair loss compared to 11 of 143 (8%) age-matched nonhirsute controls. However, in a large series of 1000 women with hyperandrogenism, only 4% had hair loss, whereas 75% showed hirsutism.³⁴

Genetics

Less is known of the inheritance of pattern hair loss in women than in men but published genetic models have generally assumed that male balding and female pattern hair loss are the same entity. Osborn proposed that balding in men and in women is attributed to a single gene with two alleles, *B* (balding) and *b* (non-balding).³⁵ She suggested that balding occurs in homozygous (*BB*) and heterozygous (*Bb*) men but only in homozygous (*BB*) women. However, in a critique of the published data, Kuster and Happle argued that the predisposition to balding is a polygenic trait in which clinical expression represents a threshold effect.¹⁹ They suggested that the threshold is higher in women because of their lower androgen levels, and women, therefore, need a stronger genetic component than men in order for hair loss to occur. In the only other published study of family histories in balding women other than that of Osborn, Smith, and Wells, found that first degree male relatives showed an increased frequency of balding compared with the male relatives of non-balding women.³⁶ In a case control study Yip and colleagues found a weak statistically insignificant association between a variant region of the aromatase gene and female pattern hair loss.³⁴

Environmental factors

In a twin study, using the Danish Twin Registry, Gunn and colleagues found a strong genetic contribution to frontal

hairline recession and hair graying in women.³⁷ However, unexpectedly the data suggested that hair thinning was not genetically determined. The study participants were elderly and none showed hair loss greater than Ludwig I. The findings may, therefore not be applicable to early onset FPHL. However, they raise the possibility that environmental factors, as yet unknown, contribute to hair loss in older women.

ALOPECIA AREATA

Alopecia areata is a chronic inflammatory disease that affects the hair follicle and sometimes the nails. It is generally thought to be a T cell-mediated autoimmune disease, although the poor response to immunosuppressive therapies casts some doubt on this idea. The onset may be at any age and male and female are probably equally affected.

Epidemiologic information on alopecia areata is limited because only one formal population study of the disorder has been published.³⁸ This examined the occurrence of alopecia areata in Olmsted County, Minnesota, USA from 1975-1989, where the incidence rate was 0.1-0.2% with an estimated lifetime risk of 1.7%.

Genetic Factors

Alopecia areata is more common in family members of affected individuals than in the population at large, although the reported frequency of a positive family history varies widely between published series from around 4% to 28%.³⁹ The risk of developing alopecia areata is probably increased by the presence of a family history. Van der Steen and colleagues calculated the risk of alopecia areata in the children of a proband at around ten-fold greater than that in the general population.⁴⁰ Colombe et al. found that a family history was more common in individuals developing alopecia areata before the age of 30 (37% compared to 7.1% in cases with onset after 30).⁴¹ In a series of 513 patients, Goh et al. found that those with more than one affected relative were more likely to have severe forms of alopecia areata.⁴²

The predisposition to alopecia areata is polygenic. Case control studies have identified a number of genes associated with alopecia areata (Table 55-1). The majority are involved in regulating immune and inflammatory responses and associate with disease severity. The most consistent relationship is with Class II MHC genes where both positive and negative associations have been reported. Alopecia areata is particularly common in Down syndrome, 8% in the series reported by du Vivier,⁴³ suggesting involvement of genes on chromosome 21. In the rare autosomal dominant disorder autoimmune polyglandular syndrome Type 1 (APS-1), over 30% of sufferers develop alopecia areata as well as other autoimmune disorders. APS-1 is caused by a mutation in the Autoimmune Regulator (AIRE) gene, which lies within the Down critical region on

TABLE 55-1—Gene Associations in Alopecia Areata

Case-controlled studies		
MHC genes		
Gene / Allele		Investigator
Positive associations		
HLA-DR4	HLA-DRB1*0401	Frentz <i>et al</i> ⁷⁶ De Andrade <i>et al</i> ⁷⁷ Entz <i>et al</i> ⁷⁸ Colombe <i>et al</i> ⁷⁹
HLA-DR5	HLA-DR11 (DRB1*1104)	Frentz <i>et al</i> ⁷⁶ Welsh <i>et al</i> ⁸⁰ Colombe <i>et al</i> ⁴¹ Marques Da Costa <i>et al</i> ⁸¹ Barahmani <i>et al</i> ⁸² Welsh <i>et al</i> ⁸⁰
HLA-DR6		De Andrade <i>et al</i> ⁷⁷
HLA-DR52b (DRB3*0202)		Barahmani <i>et al</i> ⁸²
HLA-DQ2	HLA-DQB1*0202	Barahmani <i>et al</i> ⁸²
HLA-DQ3 (HLA-DQB1*03)	HLA-DQB1*0301 (DQ7) HLA-DQB1*0302 (DQ8) HLA-DQB1*0601 HLA-DQB1*0603 HLA-DQB1*0604	Colombe <i>et al</i> ⁷⁹ Akar <i>et al</i> ⁸³ Kavak <i>et al</i> ⁸⁴ Welsh <i>et al</i> ⁸⁰ Barahmani <i>et al</i> ⁸² Morling <i>et al</i> ⁸⁵ De Andrade <i>et al</i> ⁷⁷ De Andrade <i>et al</i> ⁷⁷ Xiao <i>et al</i> ⁸⁶
HLA-DQA1	HLA-DQA1*0104 HLA-DQA1*0606	Xiao <i>et al</i> ⁸⁶
Class I chain-related gene A (MICA)		Barahmani <i>et al</i> ⁸²
Notch 4		Tazi-Ahnini <i>et al</i> ⁸⁷
Protective associations		
Other Gene Associations	HLA-DRB1*03	Akar <i>et al</i> ⁸³ Entz <i>et al</i> ⁷⁸ Barahmani <i>et al</i> ⁸²
PTPN22 – R620W variant		Kemp <i>et al</i> ⁸⁸ Betz <i>et al</i> ⁸⁹
AIRE (Autoimmune Regulator)		Wengraf <i>et al</i> ⁹⁰
IL-1 receptor antagonist		Tarlow <i>et al</i> ⁹¹
Genome-wide association study		
CTLA4		Petukhova <i>et al</i> ⁴⁵
ICOS		
IL-21/IL-2		
IL2RA		
ULBP3		
ULBP6		
STX17		
PRDX5		
Eos		

Genome-wide association study

ERBB3		
MICA		
Notch4		
BTNL2		
HLA-D		

chromosome 21. Variant regions within the AIRE gene associate with disease severity in sporadic cases of alopecia areata.⁴⁴

The association of alopecia areata with the MHC region has been confirmed in a genome-wide association study.⁴⁵ This study also identified associations with several other genes involved in predisposing to autoimmune disease, including those controlling activation and proliferation of regulatory T cells (T_{reg} cells), cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*), interleukin genes, and with regions containing genes expressed in the hair follicle (*PRDX5* and *STX17*). There was a region of strong association within the *ULBP* gene cluster on chromosome 6q25.1, encoding activating ligands of the natural killer receptor NKG2D, which has not previously been implicated in autoimmune disease.

The genetic predisposition to alopecia areata is likely to involve complex haplotypes. For example, alopecia areata in APS-1 is associated with carriage of HLA-DRB1*04 and HLA-DQB1*0302.⁴⁶

Prognosis

Most information available on risk factors in alopecia areata relates to prognosis rather than to development of the disease.

Disease severity is the most reliable indicator of prognosis. From their population study, Savaki and colleagues estimated that around 8% of affected individuals developed chronic disease.³⁸ Ikeda reported that approximately 80% of patients with patchy hair loss regrew their hair within 12 months, although the provenance of her cases was not described.⁴⁷ Most published data on the prognosis of alopecia areata, however, comes from secondary and tertiary referral centers, and is therefore biased towards the more severe end of the disease spectrum. Tosti and colleagues reported that only half of those presenting to their department with patchy hair loss were disease-free 15–20 years later and that 25% had progressed to alopecia totalis (AT) or universalis (AU). In patients presenting with AT/AU 33 out of 38 still had severe disease and only one was disease-free.⁴⁸ Previously, Walker and Rothman reported that a third of 230 patients followed for 5 years failed to recover from the original attack and all patients followed for 20 years had at least one recurrence.⁴⁹ Similar results were reported by Gip and colleagues in a 10-year follow-up study.⁵⁰

Several large case series have emphasized the unfavorable prognosis when onset of alopecia areata occurs during childhood.^{42,49,51–53}

Published rates of nail involvement vary widely, perhaps reflecting the nature of the investigators' practice but is probably around 20–30% in patients seen in specialist centres.^{54–56} Onychodystrophy is more common in alopecia totalis and universalis than in patchy alopecia.^{48,56,57}

A number of studies have reported an association between alopecia areata and atopic disease,^{47,51,52} although this has not been found by all investigators.^{55,58} In a large controlled study Barahmani et al. found that a history of any atopic disorder was associated with an overall increased risk of alopecia areata, especially the more severe forms (AT and AU), with the risk increasing particularly with atopic dermatitis.⁵⁹ Having more than one atopic disease did not increase the risk. Betz and colleagues reported that atopic subjects with alopecia areata who carried loss-of-function mutations in the filaggrin gene had a highly significant increased risk of severe alopecia compared to atopics without filaggrin mutations.⁶⁰

Other prognostic indicators include an ophiasis pattern of hair loss,⁵³ loss of body hair, and failure to respond to contact immunotherapy.

CICATRICIAL ALOPECIA

This category includes a diversity of diseases with different etiologies but with the common outcome of follicular deletion. Cicatricial alopecias are divided into primary and secondary forms. In the latter group, hair follicles are destroyed as a result of a general insult to the skin such as thermal injury, trauma, or inflammatory skin disease, and will not be considered further. In the primary cicatricial alopecias, such as lichen plano-pilaris and discoid lupus erythematosus, the hair follicle is the primary target of the disease process. There is recent evidence implicating reduced hair follicle expression of the transcription factor peroxisome proliferator-activated receptor (PPAR) gamma in the pathogenesis of lichen plano-pilaris.⁶¹

Primary Cicatricial Alopecias

The risks predisposing to primary cicatricial alopecias are largely unknown apart from the concentration of specific types to certain population groups.



FIGURE 55-2 Central centrifugal cicatricial alopecia

Central centrifugal cicatricial alopecia (CCCA) is almost exclusively a disease affecting women of African ethnicity (Figure 55-2). Its cause has long been a source of controversy, reflected by the changing nomenclature through ‘hot comb alopecia’⁶² and ‘follicular degeneration syndrome’⁶³ to its present less cause-specific designation. However, the concept that CCCA is caused by hair care practices remains the most likely explanation.⁶⁴ In a controlled study Gathers and colleagues found a strong association between CCA and a history of hair weaves or braiding but not with the use of chemical relaxers.⁶⁵

Frontal fibrosing alopecia (Figure 55-3) was first described by Kossard in 1994.⁶⁶ It affects the scalp margins,



FIGURE 55-3 Frontal fibrosing alopecia

predominantly the frontal hairline, and the eyebrows and is generally regarded as a variant of lichen plano-pilaris.⁵⁷ It is largely, though not exclusively, a disease of postmenopausal women. The cause is unknown but it appears to be becoming increasingly common since its first description suggesting involvement of an environmental factor, yet unidentified.

CHEMOTHERAPY ALOPECIA

Alopecia is a common complication of antimitotic chemotherapy (Table 55-2). Hair shedding typically occurs within 1 to 3 weeks and is complete within 1 to 2 months after initiation of chemotherapy. In most cases hair loss is temporary and recovers fully within a period of months following cessation of the causative insult. A wide variety of anticancer drugs will cause hair loss with frequencies differing for the four major classes – more than 80% for antimicrotubule agents, e.g. paclitaxel, 60–100% for topoisomerase inhibitors, e.g. doxorubicin, more than 60% for alkylating agents, e.g. cyclophosphamide, and 10–20% for antimetabolites (e.g. 5-fluorouracil). The risk of chemotherapy alopecia is also related to the particular therapeutic protocol and is greater if treatment combines two or more antimitotic agents. (reviewed in⁶⁸).

TABLE 55-2—Cytotoxic Agents and Hair Loss

Cytotoxic agents that commonly cause hair loss

Adriamycin	Docetaxel
Daunorubicin	Paclitaxel
Etoposide	Ifosfamide
Irinotecan	Vindesine
Cyclophosphamide	Vinorelbine
Epirubicin	Topotecan

Cytotoxic agents that sometimes cause hair loss

Amsacrine	Vincristine
Cytarabine	Vinblastine
Bleomycin	Lomustine
Busulphan	Thiotepa
5-fluorouracil	Gemcitabine

Cytotoxic agents that rarely cause hair loss

Methotrexate	Procarbazine
Carmustine	6-mercaptopurine
Mitoxantrone	Streptozotocin
Mitomycin C	Fludarabine
Carboplatin	Raltitrexate
Cisplatin	Capecitabine

(From Trueb RM. Chemotherapy-induced alopecia. *Semin Cutan Med Surg*. 2009;28:11–4.)

Permanent Alopecia

Although chemotherapy alopecia is usually reversible, this is not always the case. In particular, permanent alopecia is well-described following high-dose chemotherapy conditioning prebone marrow transplantation. The alopecia most commonly affects scalp hair, but permanent alopecia of eyelashes, eyebrows, axillary, and pubic hair has been reported.⁶⁹

Regimens incorporating busulphan, a drug that is widely used in patients undergoing allogeneic or autologous bone marrow transplantation, seem most likely to cause permanent alopecia.^{69–72} The extent of the alopecia appears to be dose related, but there is no clear threshold over which all patients treated with busulphan will develop permanent alopecia.⁷¹

Although busulphan is considered the main culprit of permanent alopecia, it can be seen across the spectrum

of diseases, transplant types, and with nonbusulphan containing regimes.⁷² Other chemotherapy agents have been implicated in causing permanent alopecia. De Jonge et al. reported incomplete scalp hair regrowth and permanent hair loss in patients who received high-dose chemotherapy with combination therapy of cyclophosphamide, carboplatin, and thiotepa (CTC).⁷³ The permanent hair loss was associated with having had more than one course of treatment. Vowels and colleagues⁷⁴ reported chronic graft versus host disease (GVHD) is a risk factor for alopecia, but this association was not reproduced in a later study.⁷¹ Cranial irradiation in association with busulphan was also found to increase the rate of alopecia.⁷⁴

There has been one report of permanent hair loss in women receiving treatment with taxanes for breast cancer.⁷⁵

What We Know

- The risk of developing male pattern hair loss is determined largely by a genetic predisposition. The relative contribution of paternal and maternal genes has not been established but balding in the father is a strong predictor of balding in male offspring. Variants in increasing number of genes are associated with male balding, in keeping with the concept of a polygenic predisposition.
- Less is known about risks predisposing to female pattern hair loss. There is limited evidence implicating genetic factors but a recent study suggests there is also an environmental influence on hair thinning in elderly women. Female pattern hair loss is associated with hyperandrogenism in some women, although less common than hirsutism, and many women with pattern hair loss do not show clinical or biochemical evidence of androgen excess.
- A family history of the disease is a weak predictor of the risk for developing alopecia areata. The strongest risk factor of an adverse prognosis is disease severity at presentation. Onset in childhood, nail involvement, and ophiasis are also associated with a less favorable prognosis. A large number of genetic associations have been reported with alopecia areata, especially immune response genes. Most are associated with more severe forms of the disease.
- Central centrifugal cicatricial alopecia is largely confined to women of African ethnicity. There is some evidence that it is related to hair care practices.
- Frontal fibrosing alopecia mainly affects postmenopausal women. Its cause is not yet known.
- Many antimitotic drugs cause temporary hair loss. Permanent alopecia may follow conditioning treatment for bone marrow transplantation, particularly when busulphan is used.

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Risk Factors for Occupational Contact Dermatitis

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OCCUPATIONAL CONTACT DERMATITIS

The skin serves as a protective barrier and provides a physiologic first-line of defense against various environmental influences. In this role as a protective barrier, the skin can be directly injured, or damaged by environmental exposures such as irritants or serve as a conduit and site for immunologic reactions to cutaneous allergens. Common sources of environmental exposures to the skin can be found within the work environment. Within this environment, there are a myriad of potential exposures including physical insults, biologic organisms, and chemical exposures. Within the occupational environment, skin injury, damage, and immunologic reactions manifest on the skin surface, and can result in skin diseases, which include irritant contact dermatitis, allergic contact dermatitis, as well as contact urticaria.

Contact dermatitis is the most common occupational skin disease and epidemiologic data show that contact dermatitis comprises 90 to 95 percent of all occupational skin diseases.¹ Occupational contact dermatitis is an inflammatory skin condition caused by skin contact with an exogenous agent or agents found in the workplace. Contact dermatitis can be divided into two general categories based upon the exposure, etiology, and pathophysiology of the resulting skin disease. These are irritant contact dermatitis (ICD) and allergic contact dermatitis (ACD).

Irritant contact dermatitis (ICD) is a nonimmunologic reaction to chemical irritants resulting in a cutaneous inflammation from a direct cytotoxic effect of a chemical agent. ACD is a reaction to allergens and is a type IV, delayed or cell-mediated, immune reaction. Over 57,000 chemicals can cause skin irritation, and about 3,700 chemicals have been identified as skin allergens.² Most everyone exposed to a skin irritant will develop an ICD. Allergens usually are low-molecular-weight chemicals that act as haptens, and usually only a small percentage of people will develop ACD after contact with these haptens.

Both ICD and ACD can have similar clinical manifestations and both can be evident as an acute, subacute, or chronic condition (Figures 56-1 thru 56-3). The skin initially becomes erythematous and symptoms can include



FIGURE 56-1 Acute contact dermatitis from exposure to the strong irritant, ethylene oxide.

stinging, burning, and pruritus. The skin can later develop papules or vesicles and bullae. With time, a crusting or scaling of the skin surface can develop. If there is no further exposure to the etiologic agent, the dermatitis usually resolves in 1 to 3 weeks. However, with chronic or repeated exposure, deep fissures, extensive scaling, and hyperpigmentation can occur.

The parts of the body most commonly affected include the exposed areas of the skin, such as hands and forearms,



FIGURE 56-2 Subacute dermatitis from the rubber accelerator, mercaptobenzothiazole, from the rubber in a work boot.



FIGURE 56-3 Chronic dermatitis from exposure to kerosene, a solvent that was used for cleaning the skin.

which have the greatest contact with irritants or allergens. Over 80 percent of occupational contact dermatitis involves the hands.^{2,3}

RISK FACTORS

A risk factor, as it applies to diseases such as occupational contact dermatitis, is defined as a variable associated with an increased risk of developing that specific disease. It is important to note that in many circumstances, risk factors are correlational and should not necessarily be considered as direct etiologic causes of the disease in question. Ideally, risk factors are determined by evaluating and comparing the risk of disease in those exposed to or possessing that potential risk factor to those not exposed or those without those attributes.

Understanding risk factors for a disease is important in the potential prevention of that disease state. Some risk factors often associated with diseases are endogenous factors and may be beyond the control of the individual. These include age, gender, race, and heredity/genetics. In these circumstances, an understanding of risk factors can lead to an increased awareness of one's risk of a disease. In some cases risk factors, including those considered to be exogenous, can be modified, treated, or controlled and aid in preventative measures. Examples of these types of risk factors associated with diseases include specific exposures, such as workplace chemicals and smoking tobacco, high blood pressure, physical activity, and obesity.

Inherent as a primary exogenous risk factor for occupational contact dermatitis is skin contact with an irritant or a sensitizer in an occupational setting. If an irritant or allergen does not contact the skin, then there will be no skin disease. It becomes more complex in that the relatively simple risk factor of direct exposure to these substances is related to many other factors including the occupation, the specific work duties, the work environment, the work practices, and experience level of the worker, and the protective measures used. Add to these the further complexity of

the susceptibility of an individual with "sensitive" skin or one susceptible to developing allergic reactions. Many of these risk factors have been poorly studied and are not well described.

Data on occupational contact dermatitis risk factors are limited and all sources have their limitations. Information on risk factors for occupational contact dermatitis comes from a variety of sources including occupational disease and injury surveys, workers' compensation records, specific workplace investigations, clinical investigations (e.g., patch test studies), and clinical case studies. It can be difficult to obtain full information on risk factors associated with occupational contact dermatitis for a variety of reasons, many of which are inherent in the disease process. These include: (1) lack of a clear and consistent case definition for the disease; (2) difficulty of definitive diagnosis as to etiology and work-relatedness; and (3) in many cases the disease goes untreated or is not evaluated by a health care professional.

In particular, the work-relatedness of contact dermatitis may be difficult to prove. The accuracy of the diagnosis is related to the skill level, experience, and knowledge of the health professional who makes the diagnosis and confirms the relationship with environmental or workplace exposures. Guidelines are available for assessing the work-relatedness of dermatitis, but even with guidelines, the diagnosis may be difficult.⁴ The diagnosis is based on the medical and occupational histories and physical findings. The importance of the patient's history of exposures and disease onset is clear. Standardized questionnaires for surveying work-related skin diseases are available and can be helpful in the workplace.⁵ In ICD, there are no additional confirmatory tests. In many instances, ACD can be confirmed by skin patch tests using specific standardized allergens or, in some circumstances, by provocation tests with nonirritating dilutions of industrial contactants. ICD may be overestimated (and allergic contact dermatitis underestimated) because of time, expense, and availability of skin patch testing; physician experience; and the limited availability of allergens in the United States (US).

Occupation as a Risk Factor

Specific national occupational disease and illness data are available from the U.S. Bureau of Labor Statistics (BLS), which conducts annual surveys of approximately 176,000 employers selected to represent all private industries in the United States.⁶ All occupational skin diseases or disorders, including contact dermatitis, are tabulated in this survey. BLS data show that occupational skin diseases consistently accounted for 30 to 45% of all cases of occupational illnesses from the 1970s through the mid-1980s, and in recent years accounted for nearly 18 percent of all occupational illness.⁶

U.S. Bureau of Labor Statistics data for occupational skin diseases for 2002 to 2007 are shown in Table 56-1.

TABLE 56-1—Numbers and Rate of Occupational Skin Diseases Per Year, United States, BLS Survey Data 2002–2007⁶

Year	Number of cases (000's)	Incidence rate per 100,000
2002	44.9	51
2003	43.4	49
2004	38.9	44
2005	40.1	44
2006	41.4	45
2007	35.3	37

However, because of BLS survey limitations it is thought that these data underestimate the actual number of occupational skin diseases. In 2007, BLS estimated 35,300 cases of occupational skin diseases or disorders in the U.S. workforce for an annual incidence rate of 37 cases per 100,000 workers.⁶ Total numbers and incidence rates of occupational dermatologic conditions, by major industry division, based on the BLS survey for 2007 are shown in Table 56-2. The greatest number of cases of occupational skin diseases is seen in manufacturing, but the highest incidence rate is seen in the industrial sector of agriculture, forestry, fishing, and hunting.

In 1988, the National Health Interview Survey (NHIS) included an Occupational Health Supplement, which included questions on dermatitis. Although dated and scheduled to be updated in 2010, the 1988 Occupational Health Supplement offers the most complete data available in the United States for specific information on

self-reported dermatitis. The survey consisted of personal interviews of people in randomly selected households. For 30,074 people participating in the NHIS, the annual period prevalence was 11.2 percent for all dermatitis, 2.8 percent for contact dermatitis, and 1.7 percent for occupational contact dermatitis. Projecting these results to the U.S. working population resulted in an estimate of 13.7 million people with dermatitis, 3.1 million people with contact dermatitis, and 1.9 million people with occupational contact dermatitis.⁷

In the NHIS, the occupational groups with the highest prevalence of self-reported occupational contact dermatitis included physicians, dentists, nurses, pharmacists, and dieticians (5.6%); public transport attendants, cosmetologists, and other personal service occupations (4.9%); health care therapists, technologists, technicians, and assistants (3.5%); and mechanics and repairers of vehicles, engines, heavy equipment, and machinery (3.5%).⁷

An analysis of Oregon workers' compensation claims data for 1990 through 1997 estimated the average claim rate of occupational dermatitis to be 5.7 per 100,000 workers. In this 8-year period, 727 workers' compensation claims were filed for occupational dermatitis, of which 611 were determined to be compensable.⁸ Of all accepted workers' compensation claims for occupational contact dermatitis in Oregon, the occupations with highest claim rates were farming, fishing, and forestry workers (18.2%); machine operators and assemblers (16.5%); service-related workers (15.3%); laborers (13.7%); precision production crafts workers (8.0%); and protective services workers (5.7%), followed by technicians and related support workers, transportation and material movers, and professional specialty, administrative support, executive, administrative, and sales employees.⁸ Self-employed individuals, such as hairdressers and cosmetologists, are not represented in these claims.

TABLE 56-2—Numbers and Incidence of Occupational Skin Diseases by Industry Sector, 2007 BLS Survey Data⁶

Industry Sector	Number of cases	Incidence rate per 100,000
Agriculture/forestry/fishing/hunting	1200	123
Manufacturing	8800	62
Education and Health Services	7700	57
Leisure and Hospitality	4100	46
Construction	2600	36
Professional and Business Services	3600	26
Other services	800	26
Trade/transport/utilities	5500	24
Information	400	17
Mining	<100	13
Financial Activities	600	8
TOTAL	35,300	37

Exposure as a Risk Factor

The irritating potential of a substance is dependent on a variety of factors including physical and chemical properties, concentration and dose as well as exposure duration and occlusion. The etiology of ICD is often multifactorial, but the most common skin irritant is wet work, defined as exposure of skin to liquid for more than 2 hours per day, use of occlusive gloves for more than 2 hours per day, or frequent handwashing.⁹ Other common causes of ICD include soaps and detergents, solvents, food products, cleaning agents, plastics and resins, petroleum products and lubricants, metals, and machine oils and coolants.⁹ Frictional ICD can be caused by low humidity, heat, paper, tools, metals, fabrics, plastics, fibrous glass and other particulate dusts, and cardboard, among other causes.¹⁰

The induction and elicitation of sensitization and the resulting clinical picture of ACD is dependent on a complex process of exposure to a low-molecular-weight chemical, penetration of that chemical through the skin,

TABLE 56-3—North American Contact Dermatitis Group Patch-Test Results, 2003 to 2004¹³**Prevalence of 20 most common positive reactions (n varies from 5106 to 5145)**

<i>Test Substance</i>	<i>Common sources</i>	<i>% Positive</i>
Nickel sulfate 2.5% pet	Metals, jewelry	18.7
Neomycin sulfate 20% pet	Creams, lotions	10.6
Myroxylon pereirae (balsam of Peru) 25% pet	Fragrance chemicals	10.6
Fragrance mix 8% pet	Toiletries, scented products	9.1
Quaternium-15 0.5% pet	Cosmetics, sunscreens	8.9
Sodium gold thiosulfate 0.5% pet	Jewelry, dental products	8.7
Formaldehyde 1% aq	Fabrics, skincare products	8.7
Cobalt chloride 1% pet	Metals, jewelry	8.4
Bacitracin 20% pet	Ointments, creams	7.9
Methyldibromo glutaronitrile phenoxyethanol 2.5% pet	Biocides, skincare products	6.1
p-Phenylenediamine 1% pet	Hair dyes, leather	4.7
Thiuram mix 1% pet	Rubber, pesticides	4.6
Potassium dichromate 0.25% pet	Cement, leather	4.3
Carba mix 3% pet	Rubber, pesticides	4.0
Diazolidinylurea 1% pet	Skin care products	3.5
Propylene glycol 30% aq	Cosmetics, topical meds	3.3
Imidazolidinylurea 2% pet	Skin care products	2.9
Colophony 20% pet	Glues, adhesives	2.8
Tixocortol-21-pivalate 1% pet	Corticosteroids	2.7
Diazolidinylurea 1% aq	Skin care products	2.5
Ethylenediamine dihydrochloride 1% pet	Dyes, rubber, fungicides	2.4

protein reactions, and a cascade resulting in a cell-mediated immune response. The major factors related to this process and inherently related to the exposure parameters include potency of the allergen, dose per unit area of skin exposed, duration and frequency of that exposure, vehicle, and occlusion of the chemical.¹¹ Contact allergens show both threshold and dose-response characteristics and potential sensitizing risks of substances have been graded using the murine local lymph node assay.¹²

Common causes of ACD include plants, such as poison ivy, poison oak, and poison sumac, metals, biocides, epoxy resins, rubber additives, and fragrances. The most common skin patch test allergens found to be positive in patients along with potential sources of exposure are shown in Table 56-3.¹³ In patients with occupational contact dermatitis who were skin-patch tested, the most common relevant allergens included thiuram mix, carba mix, bacitracin, methyldibromo glutaronitrile/phenoxyethanol, formaldehyde, glutaraldehyde, methylmethacrylate, nickel, cobalt, and chromium.^{14,15}

Work Practices as Risk Factors

Protective gloves and clothing can reduce or eliminate skin exposure to hazardous substances if used correctly. However, if used improperly or selected poorly there is a

danger of increasing permeation and penetration of irritants and allergens through the occlusion induced by contaminated gloves or clothing. In addition, glove or clothing components may directly irritate the skin or contain allergens, such as latex or rubber additives, so the correct use of personal protective equipment is at least as important as their selection.¹⁶ Similarly, the excessive pursuit of personal hygiene in the workplace may actually lead to misuse of soaps and detergents and resulting ICD. Proper handwashing methods and adequate moisturizing is valuable in preventing contact dermatitis.³ The effectiveness of barrier creams is controversial because there are limited data on the protective nature of these topical products during actual working conditions involving high-risk exposures. Educating the workforce about skin care, exposures, and personal protective equipment use is an especially important measure in the prevention of occupational contact dermatitis.

Age, Race, and Gender as Risk Factors

It is difficult to view age as an independent risk factor for occupational ICD and ACD. For example, age plays a role in job seniority and the potential transitioning of job duties and therefore exposure, skin hardening, the learning curve of job-related best practices to protect the skin, and the healthy worker effect. When looking at skin irritation

responsiveness, there are reports that older individuals have a reduced reactivity to irritants.¹⁷ Information on occupational ACD is less clear, although there have been immunologic changes described with age.

Racial differences in the skin and the reaction of the skin have been described, although it has been difficult to draw definitive conclusions as to their applicability in the clinical setting. African American skin types have been found to have an increased number of layers of the stratum corneum, are more resistant to the effects of tape stripping, have higher lipid contents and elasticity compared to other skin types.¹⁸ However, there still are conflicting findings as to susceptibility of skin irritation and sensitization. There is some evidence that Asian skin may be more reactive and Black skin less reactive than Caucasian skin.¹⁹

In many studies, occupational ICD is seen more often in females. Epidemiologic assessments, which may be biased by chemical exposure patterns and specific gender-related occupations, give a perception that females are more reactive to irritants than males, however this is not necessarily supported by direct comparative testing.¹⁷ Similarly, females may be more predisposed to develop ACD, but again this is likely related to exposure patterns and not to intrinsic skin characteristics.²⁰

Genetics and Atopy as Risk Factors

Variations in genes play a role in skin barrier function and inflammatory mediators. Genetic susceptibility markers have been found for both ICD and ACD affecting the production of proinflammatory cytokines interleukin (IL)-1 α , IL-1 β , IL-8 and tumor necrosis factor (TNF- α), and anti-inflammatory IL-10.²¹ In addition, mutations in the filaggrin gene, which result in impaired skin barrier functions have been identified as risk factors for atopic dermatitis and possibly for ICD and ACD. Polymorphisms in genes encoding for metabolic enzymes, such as

N-Acetyltransferases, play a role in ACD.²¹ Studies in twins show that monozygotic twin pairs have a higher risk of hand eczema when compared to dizygotic twins.²¹

Atopic diathesis is known to increase the susceptibility of skin to irritants but not to allergens.²¹ As a result, workers with atopic skin disease are more likely to develop occupational skin diseases, especially in occupations involving wet work and irritant chemicals.²² Also, maceration and other skin diseases which disrupt the skin barrier can enhance penetration of both allergens and irritants.

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What We Know

- Occupational contact dermatitis remains a relatively common disease with a noteworthy public health impact. These factors, along with the potential chronicity of the disorder, its effect on an individual's vocational and avocational activities, and its preventability make occupational contact dermatitis a disease of public health importance. Understanding risk factors and where applicable modifying those risk factors are key components to preventing occupational ICD and ACD. Risk factors for occupational ICD and ACD include specific occupations, exposures to specific irritants and allergens, improper work practices, genetic predispositions, and atopic diathesis. Less defined risk factors include age, race, and gender.

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Viral Infections and Skin Cancer

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I. MERKEL CELL CARCINOMA

Background

Merkel cell cancer (MCC) is considered to be a rare and aggressive neuroendocrine tumor. Approximately 30% of all MCC patients die from metastatic disease within 2 years of diagnosis. Merkel cells are normally found in the basal layer of the epidermis and near hair follicles and have features of both mechanoreceptor and neuroendocrine cells.

Risk factors for the development of MCC include sun exposure and age. In addition, there is an increased risk for developing MCC among patients who are immunocompromised. Consistent with reports that the incidence of MCC is increasing, there were an average of three cases per year from 1979 through 1999 and then 10 per year from 2000 through 2004.

Remarkably, a new human polyomavirus, which has been termed Merkel cell polyomavirus (MCPyV), was first published in 2008 to be integrated into the genome of MCC¹. Mounting evidence supports MCPyV to be involved in one pathway of MCC oncogenesis. Integrated MVC DNA has been identified in MCC tumors at both primary and metastatic tumor sites indicating integration prior to metastasis.

Multiple factors point to the role of MCPyV in MCC. MCC occurs more frequently than expected among immunosuppressed patients, indicating an infectious component, or at least a final common pathway influenced by immune dysfunction. The virus has been found to be mutated in cases of MCC where it is integrated; it loses its ability to replicate and cause cell lysis, but still maintains other gene functions which effect cell cycle progression.

EPIDEMIOLOGY

MCC occurs mostly in Caucasians between 60 and 80 years of age. It occurs about twice as often in males as in females. Researchers believe that exposure to sunlight or ultraviolet light may increase a person's risk of this disease.

Historically MCC has been viewed as having low 5-year survival rates ranging from 29% to 64%. Currently, a 4-tiered system is widely used that separates the patients with localized cutaneous disease based on the largest clinically assessed diameter of the primary tumor (<2 cm or > 2 cm). Lymph node-negative disease with a tumor <2 cm is classified as stage I, lymph node-negative disease with a tumor >2 cm is classified as stage II, lymph node-positive disease is classified as stage III, and the presence of distant metastatic disease is categorized as stage IV. Although low-stage disease predicts a relatively good prognosis, it is not an optimal indicator, because approximately 20% of patients with clinical stage I MCC will die of disease within 5 years of diagnosis².

TREATMENT

MCC is known to be both radio- and chemosensitive. Patients are generally treated with surgery as a first-line therapy, supplemented with adjuvant radiotherapy and chemotherapy if required. The use of adjuvant therapies in MCC is under debate.

Stage-specific treatment regimens have been outlined involving various combinations of surgery, radiation and chemotherapy for International Union Against Cancer (UICC) stage I to III disease while the emphasis of treatment in patients with UICC stage IV disease is on palliative care with or without radio- or chemotherapy. There is a need for more structured clinical research to better illuminate the most effective treatments for this disease³. In part due to the rarity of the disease, prospective randomized clinical trials are lacking.

SEARCH METHODOLOGY

The Cochrane Library for systematic reviews (2009) and Pubmed/Medline (1976–September 2009) were searched for prognostic outcomes for MCC. The following questions were formulated, and additional cross-references were performed under each sub-category.

What is the prognosis of MCC associated with the merkel cell associated polyomavirus (MCPyV) versus without it?

MCPyV is believed to have a role in the development of a substantial portion of MCC tumors. Approximately 80% of MCC evaluated for MCPyV, have shown evidence of this virus integrated in a monoclonal pattern, indicating viral DNA integration into the host precursor cell prior to oncogenesis¹. MCPyV has not been demonstrated in at least 20% of MCC tumors suggesting a distinct etiopathogenesis. Like other tumor viruses, some people who demonstrate prior infection, even with genomic evidence of MCPyV clonal integration, do not develop MCC. Currently it is not clear what other factors are necessary for MCC oncogenesis. Intriguingly, the MCPyV obtained from tumors has specific mutations that render the virus uninfected and even replication incompetent⁴. The significance of this relates to the mutated viruses' ability to transform the cell without causing cell destruction, which is a common component in viral associated cancers.

One retrospective study has been published looking at the prognosis of MCC with and without associated MCPyV. Data was evaluated from 1979 to 2004 in Finland. The national cancer registry in Finland is known for its quality, making this data nearly representative of all MCC cases diagnosed within this 26 year period⁵. This yielded 114 cases of MCC that were analyzable for the presence of viral DNA by polymerase chain reaction (PCR) amplification for viral detection as well as viral quantification. MCPyV DNA was detected in 91 (79.8%) of the 114 MCCs tested. The quantity of viral DNA was found to vary between a few copies per 10, 000 cells to more than 4000 copies per cell. The majority of MCCs had a substantial amount of viral DNA, and only 9 of those 91 MCC with associated MCPyV DNA, had less than one copy of viral DNA per 10 cells. In addition to the detection of viral DNA, this study evaluated the prognosis of the MCCs associated with and without DNA. Those MCC that were found to have MCPyV DNA had a better prognosis than those without the associated viral DNA (5-year survival 45% vs 13% respectively; P < .001, two-sided log-rank test).

Additionally in this study it was noted that the extremities were most frequently affected by the MCC with associated MCPyV DNA. This has been found in other studies and has been postulated to be associated with UV exposure by some, while others have hypothesized a link between UV exposure and viral oncogenetic activation in virally associated cancers. Also of note in this and other studies was that the MCC associated with MCPyV DNA and those MCC without MCPyV DNA, were indistinguishable from one another on histology.

In another quantitative PCR for MCPyV, as well as immunohistochemical staining of tumor cell proteins, retinoblastoma gene product (pRb) and terminal deoxyribonucleotidyl transferase (TdT) were evaluated. MCPyV

was detected in 19 of 23 (74%) primary MCC tumors, but 8 of these had less than 1 viral copy per 300 cells. Interestingly those tumors with higher viral abundance were associated with longer survival (p < or = 0.08) (and less p53 expression). Their data suggested that MCC might arise through several oncogenic pathways, including ones independent of MCPyV. This also lends some support to improved prognosis of MCC with the association of MCPyV⁶.

Limitations

This study did not address whether there were mutations present, as previously seen in specific MCPyV sequences in relation to prognosis. It was also not evaluated if the viral DNA was integrated into the host chromosome, because PCR cannot distinguish episomal from integrated viral DNA. In addition there was no analysis by stage of tumor at diagnosis, or any correction for other clinical factors such as treatment which may have affected outcomes.

Conclusion

Studies have shown that MCPyV DNA is widespread and the genomic presence and associated mutations are being studied to further uncover the significance of its presence in a majority of MCC. Future retrospective and prospective treatment studies may improve understanding of this topic of prognosis of MCC and viral DNA, and take into account stage at diagnosis as well as treatment modalities.

What is the prognosis of MCC as stratified by demographic and clinical features?

According to a retrospective evaluation and smaller studies, there are several demographic and disease factors which portend a poor prognosis with MCC. These include male sex, age greater than 70 years at diagnosis, size >1 cm, the number of positive lymph nodes, metastatic dissemination, presentation with recurrent disease, and the presence of residual disease during radiation treatment⁷. While most studies have found most of the demographic and clinical features to affect prognosis some studies, such as one by Guler et al. reported that parameters such as sex, site of tumor, sentinel node biopsy, excision margins, skin and non-cutaneous malignancies were not found to be significant for survival outcomes⁷.

In a large meta-analysis, stage of disease has been shown to be an independent predictor of survival (P < 0.03) and disease-specific survival.³

This finding was seen in multiple other studies evaluating prognosis in patients with MCC. One study even reported that prognosis based upon stage was independent of treatment modality. Lewanda et al. found in their study that even amongst different treatment groups, the Kaplan-Meier survival curves leveled off at 30 months with 82%

survival for the stage I/II group and at 19 months with 60% survival for the stage III group⁸.

The importance of stage on prognosis has been evaluated in several different ways including overall survival outcomes and tumor-specific survival. Guler et al. reported that the stage of the disease and age at initial presentation were statistically significant with regard to overall ($P < 0.0001$; $P = 0.0327$) and tumor-specific survival ($P < 0.0001$; $P = 0.0156$). Use of the Cox regression model revealed initial stage of the disease as the only significant factor in their multivariate analysis⁷. While the majority of studies have reported stage at diagnosis to be a predominant factor in prognosis, however, another studies did not support this⁹.

A meta-analysis also determined that the stage of disease at diagnosis affected prognosis with MCC. Stage I and stage II disease have good prognostic outcome measures, while those with stage III and IV had significantly worse survival outcomes³. The demographic and other clinical features aside from staging which have demonstrated prognostic importance for MCC are male sex, increasing age, tumor size, metastasis, and evidence of initial treatment failures³.

What is the prognosis (5 year survival) of MCC based upon treatment modalities?

MCC has a high rate of recurrence after treatment. In part due to the uncommon nature of MCC, there is a lack of prospective controlled trials to guide management of this disease. Surgery is generally considered a first-line therapy, with adjuvant radiotherapy and chemotherapy being used in various clinical settings with variable outcomes, making the use of these therapies subject to debate. Meta-analyses of existing retrospective data suggests that adjuvant radiotherapy has a benefit on overall 5 year disease-free survival, and a reduction in local and regional recurrence rates. Results on the survival benefit and recurrence rate data with the use of chemotherapy is much more variable, and while chemotherapy appears to not improve prognosis, a clear evidence-based recommendation is difficult to take away from the existing data. Stage-specific treatment regimens have been outlined by the International Union Against Cancer (UICC) for stage I to III disease with the use of combinations of surgery, radiotherapy, and chemotherapy. The emphasis on UICC stage IV disease is on palliative care. While these recommendations are a useful tool, the evidence-based data on outcomes is variable and limited to primarily retrospective cases and cohorts, implicating a need for more structured clinical research to guide treatment.

Surgical Treatment

Surgery is usually the first treatment that a patient undergoes for MCC. Multiple retrospective reviews have been completed regarding surgical treatment of MCC. One retrospective review of 95 consecutive patients treated with

wide local surgical excision demonstrated a highly variable prognosis for surgically managed early stage MCC. The primary recommendation from this analysis was that a multidisciplinary tumor-board consultation approach be utilized for optimization of individual MCC patient management. In this study clinically negative regional nodes were either followed up ($n=42$) or staged with sentinel lymph node biopsy ($n=21$). Those clinically positive nodes underwent lymph node dissection ($n=32$). A total of 45 (47%) patients relapsed. The 5-year crude cumulative incidence (CCI) of recurrence and disease-specific survival (DSS) were 52% and 67%, respectively.¹⁰

Another retrospective study looked at surgery alone for treatment by wide local excision. Wide local excision resulted in a trend of decreased local recurrence when 2 cm margins were obtained. Those tumors with at least 2 cm margins had 0% local recurrence versus < 2 cm margins had 29% local recurrence. However, overall survival was not significant between the groups, since nearly a third of all patients undergoing wide local excision still died of distant metastasis¹¹.

Another retrospective review of patients undergoing resection of primary MCC was performed. Analysis was on 213 patients that had undergone resection of the primary tumor and evaluation of the draining lymph node basin. Those patients with MCC $<$ or $=$ 1.0 cm had a low likelihood of having had regional lymph node metastasis. They concluded that surgical treatment is appropriate and that regional nodal evaluation may always be necessary in these tumors, but that their data supports sentinel lymph node evaluation for MCC more than 1 cm in diameter. Of these 213 patients, 54 patients (25%) had tumors $<$ or $=$ 1.0 cm in diameter, and only 2 of these 54 patients (4%) had regional lymph node metastasis, compared with 51 patients (24%) with tumors more than 1.0 cm ($P < .0001$) with regional lymph node metastasis. Of note both of the patients with less than 1 cm MCC had clinically evident nodal disease at presentation, and this was the reason they underwent lymph node biopsies¹².

One limitation of this study was that not all patients with MCC disease identified during their time period were included in their analysis, but rather only those patients whom had undergone surgery and regional lymph node basin evaluation. There may have been MCC cases in their time period that were below 1 cm and ended up with metastatic recurrence, but based on a different treatment modality were not included in their analysis.

Noteworthy is that in addition to primary surgical therapy, sentinel lymph node biopsy was found to have a significant outcome on survival and nearly every prognostic indicator evaluated in several meta-analyses on the subject^{3,13-15}.

Adjuvant radiotherapy

In general the retrospective data is in support of radiotherapy in conjunction with surgical removal. Possibly in

part because of the retrospective review nature, the wide differences in patient presentations, and different analyses of the data used, the results are variable.

Several articles have reported the effectiveness of surgery with adjuvant radiotherapy. A recent meta-analysis evaluated the data on adjuvant local radiotherapy compared with surgery alone for stage I and II patients only. In their subgroup analysis a significant overall (HR, 0.63; $P = .02$) and cause-specific (HR, 0.62; $P = .04$) survival advantage was demonstrated after treatment with combined surgery and radiotherapy⁷.

Another retrospective analysis of 57 patients with MCC was performed in regards to outcome measures. All of these tumors (except for one which was stage III) were initially staged as I or II. This analysis reported that radiotherapy applied after primary tumor excision extended the time to disease progression significantly ($P = 0.0376$) but did not prolong overall or tumor-specific survival⁷.

A retrospective review of 36 patients with MCC of the head and neck ranging from stage I to III at diagnosis was performed to evaluate the impact of radiotherapy on prognostic outcomes. This review demonstrated that radiation therapy to the primary tumor site resulted in a local control rate of more than 90% in patients with head and neck MCC. A trend toward improved regional control of the clinically negative neck with the addition of radiation therapy was also seen but was not found to be statistically significant⁸.

A retrospective review of 60 patients with MCC of the lower limb was performed to evaluate prognostic indicators in this group. They included patients that were treated with surgery, radiation, or chemotherapy all for curative intention. The 5-year overall survival, disease-specific survival, and relapse free survival (RFS) were 53%, 61%, and 20%, respectively. On univariate analysis the addition of any radiotherapy improved RFS ($p < 0.001$). When stratified by location of radiotherapy, both radiotherapy to the inguinal nodes ($p = 0.01$) or primary site and inguinal nodes ($p = 0.003$) were significant in regards to survival. On multivariate analysis the addition of radiotherapy (hazard ratio = 0.51, $p = 0.03$) had a significant improvement in survival over surgery alone⁹.

Two other retrospective analyses also favored the use of adjuvant radiotherapy. One found that post-excisional adjuvant radiation treatment increased the proportion of patients without recurrence as compared to surgery alone (75% vs 53%; $P = 0.02$)¹⁶. In the other study, this data was reported as less local recurrence for surgery with adjuvant post radiotherapy, i.e. 6% local recurrence, (vs 19% surgery alone)¹⁷. Similar trends were seen for regional metastatic recurrence (50% with surgery, 36% with combination treatment). The rate of distant metastasis was 25% in both retrospective treatment groups¹⁷.

Other retrospective review studies found that radiotherapy significantly increased the median relapse free survival months compared with surgery alone. This was

up to 30 months difference between the treatment groups in the study with the longest follow-up data¹⁸, but in the other two studies the relapse free survival rates were at least a factor of 2 different between groups, favoring the radiotherapy treatment group in both publications^{19,20}.

In one retrospective study with 86 patients, nodal relapse rates were significantly different amongst the two treatment groups, but local disease recurrence was not. This study specifically reported that surgery in comparison to surgery with adjuvant radiotherapy to the nodal basin had a greater nodal relapse rate (26% vs 13%)²⁰.

In a couple of other retrospective studies of surgery versus surgery with radiotherapy, no significant improvement in local recurrence rates was seen between these two groups. These studies were with 102 and 251 patients. Local recurrence rates were seen as 8-11% for radiotherapy versus 10-11% for surgery alone $P = 0.84^{21}$, $P = 0.76^{22}$.

In addition in one of these studies, while adjuvant chemotherapy did not show a survival advantage or improvement in local disease recurrence, it is noteworthy that only 15 patients had received adjuvant radiotherapy, and only 2 of these experienced local recurrence. Because of the low incident numbers in these groups, this data has limited power²².

One retrospective analysis specifically looked at Mohs surgery combined with radiation therapy. Forty-five patients were included in this analysis, which indicated that radiation therapy initiated after Mohs surgery did not have a significant affect on survival or recurrence rates when compared to Mohs surgery alone. The Kaplan-Meier disease-specific overall survival estimates by treatment groups demonstrated 5-year survival rates of 79% for Mohs surgery alone and 80% for Mohs surgery and radiation treatment²³.

While there is some variation on the outcome and prognostic data between surgery and the addition of radiotherapy, overall the data, including that from the meta-analysis, supports the use of adjuvant chemotherapy. Further studies of a randomized prospective nature may help better elucidate in which patients radiotherapy has the best benefit.

Chemotherapy

Chemotherapy has been used in certain scenarios primarily in advanced stages of MCC. An overall conclusion regarding the prognosis with chemotherapy use in the literature appears to be the most variable of all three of these treatment modalities. The data is variable in relation to chemotherapy use for MCC both in the adjuvant setting and in treatment of metastatic disease. This may in part be due to the great variability of clinical disease conditions it is used, which specific regimens are used, and that these retrospective cases were often cases of advanced disease where prognosis is already poor.

Various retrospective analyses of the utility and affect on survival of chemotherapy exist. One such study by

Poulsen et al. failed to find a clear benefit of chemotherapy over surgery alone. It was noted in the analysis that because of the wide confidence intervals, a clear conclusion could not be derived from their analysis²⁴.

Many studies indicate that salvage chemotherapy to the metastatic site does not have any significant effect on survival^{8,21,25}. There is variation in the way the data is analyzed and reported in terms of outcome and prognosis amongst these studies. For instance in one study patients with unresectable metastases were marginally responsive to chemotherapy with 12.5 % having a complete response, another 12.5% having a transient response, and 75% with no detectable response²¹.

A couple of other studies reported a negative impact on survival with the use of chemotherapy. However in one of these studies the baseline factors were adjusted for in the analysis, such as adjusting for advanced disease and alteration of expected outcomes in advanced cases²⁶. With this adjustment factor, the survival rates between chemotherapy and non-chemotherapy treatment groups were not seen to be significantly different¹¹.

Data from a meta-analysis on 107 subjects published in 1999 demonstrated no difference in response rates of first line chemotherapy between those patients with locally advanced disease versus distant metastatic MCC (69% vs 57%)²⁶. However, progression after first-line chemotherapy was associated with significantly worse survival for patients with metastasis. Rates of response to second-line (n = 33) and third-line (n = 10) chemotherapy were 45% and 20%, respectively. Their overall conclusion from this meta-analysis was that while MCC is chemosensitive, it is rarely chemocurable in patients with metastasis or locally advanced tumors²⁶.

Surgery and adjuvant radiation therapy appear to have the best supporting survival data at this time for treatment of MCC. Chemotherapy does not appear to improve survival, however, the data being compared in this area is the most variable in regards to protocols and treatments used, making evidence-based conclusions the most difficult. In addition to randomized controlled trials to better evaluate prognosis amongst treatment groups, consortia are still needed to clarify the risks and benefits of sentinel lymph node biopsy, adjuvant radiation therapy, and salvage therapies, based upon a standardized histological diagnosis and staging of MCC. Further studies are also necessary and underway regarding the etiologies of MCC and the role MCPyV plays in oncogenesis and prognosis.

See What We Know-MCC

II. KAPOSI'S SARCOMA

Background

Kaposi's Sarcoma (KS) is a tumor with an etiologic association with human herpes virus 8 (HHV8), also known as Kaposi's sarcoma-associated herpesvirus (KSHV). Background and treatment of this tumor are described in the prior chapter regarding treatment of KS. There are several types of KS, however the type we will be discussing in this chapter is the type associated with immune suppression. Prognostic factors for immune deficient and AIDS-related KS have been evaluated and used to formulate staging of the disease. The prognosis is related to the type of KS, the extent of cutaneous and visceral involvement, as well as the patient's immune status and the viral load burden. Typically KS is an indolent disease progressing

What We Know: MCC

- Merkel cell carcinoma (MCC) is a rare, aggressive skin cancer of neuroendocrine origin, most commonly seen in immunosuppressed patients and patients over 50 years of age.
- A more recently discovered Merkel Cell Polyomavirus (MCPyV) has been demonstrated in approximately 80% of MCC to date. Limited data thus far suggested that MCPyV may have a role in oncogenesis with this tumor. While it is not required for the development of all MCC, in MCC cases with associated MCPyV, limited data suggests improved survival outcomes.
- The rarity of MCC means that there is a lack of prospective controlled trials with this disease. Patients are generally treated with surgery as a first-line therapy.
- There traditionally has been some variability in which patients undergo sentinel lymph node biopsy.

The use of this procedure has been documented in multiple retrospective studies and meta-analyses to impart survival benefit.

- The use of adjuvant therapies in MCC remains controversial. Data from retrospective analyses in addition to meta-analyses suggests that the addition of radiotherapy in patients with MCC may impart significant improvement in local and regional recurrence rates as well as disease-free survival. The use of chemotherapy treatment with curative intention is less supported by the current literature.
- Stage of disease has been shown to have a significant correlation with disease free survival rates. More structured clinical research will improve the evidence-based data on the most effective treatments for this disease.

over years, with the gradual development of new sites of involvement. However KS in immunosuppressed patients may be a fulminant disease.

The tumor burden (T), the immune status (I), and the severity of the systemic illness (S) are all prognostic determinants proposed by the ATCG, which were formulated based upon prior outcome measures. This system is used in patient staging and to determine management and was proposed based upon prospective data. In the post HAART era an updated version of the ATCG system has been proposed due to data indicating that other determinants are involved in patient outcome and prognosis.

Prognosis

The most recent National Cancer Institute's SEER program data, shows an overall 5-year relative survival of about 60% for KS. When looking at patients staged by the ACTG staging system, those at low risk T and I factors combined, have a 5-year survival of 90%. For those at high risk in these categories, the 5-year survival was around 50%. It dropped to 30% if the KS was in the lungs.

Outcome measures

In addition to survival rates, other data is used to evaluate response to treatment, which affects outcome and prognostic measures. The clinical trials discussed below use the AIDS Clinical Trials Group (ACTG) Oncology Committee criteria for evaluating KS and its response to treatment. Much of the clinical response criteria has been standardized. A complete response is defined as the absence of residual KS for at least 4 weeks, a partial response as $\geq 50\%$ reduction in size or at least 50% flattening of the lesions, stable disease as not fulfilling the criteria for partial or progressive disease, and progressive disease as $\geq 25\%$ increase in size²⁷.

SEARCH METHODOLOGY

The Cochrane Library for systematic reviews (2009) and Pubmed/Medline (1976–September 2009) were searched for prognostic outcomes for randomized controlled trials with prognostic outcomes for AIDS-related KS.

What is the prognosis of AIDS associated KS based upon CD4 levels?

As briefly mentioned above, KS is staged in part based upon CD4 levels at time of KS diagnosis. I0 is considered good risk, and is defined as a CD4 cell count of 200 cells/mm³. Some of the more recent studies since the advent of HAART have used counts of either 150 or 100. I1 is

considered a poor risk, and corresponds to a CD4 cell count lower than 200 cells/mm³.

While recent studies have supported the ACTG staging determinants to be important prognostic markers which are still used in staging currently, some adjustments to the staging system have been proposed based upon prognostic data, predominantly associated with the wide use of HAART in HIV patients.

Most studies have indicated that while treatment of KS has improved, the patient's CD4+ levels remain to have a significant association with prognosis of KS. This finding has been demonstrated in several different ways by several different measurements of prognosis, but the vast majority demonstrates that prognosis is related to CD4 levels.

A study published in 1997 prospectively validated the previously established ACTG staging classification for AIDS-associated KS. Data from 8 ACTG therapeutic trials for AIDS-associated KS on 294 patients were staged prospectively according to tumor extent (T), severity of immunosuppression (I), and other HIV associated illness (S), and were observed for survival²⁸.

Survival was significantly shorter for patients in the poor-risk category for each of the TIS variables. Multivariate analysis indicated that the severity of immunosuppression gave the most predictive information. Cox models using a CD4 count of 150/ μ L rather than the previously adopted 200/ μ L to prognosticate disease based upon I0 and I1, yielded a clearer difference in prognosis in their analysis. They suggested an update of the prior staging system I category to reflect these CD4 levels. Their conclusions were that a lower CD4 count than the one originally proposed provides better discrimination between prognostic groups, and hypothesized that the advent of HAART may have affected this outcome measure²⁸.

Another retrospective study compared the clinical course of 91 patients with AIDS-related KS with CD4 counts >300 cells/mL and undetectable HIV viral loads (VLs) to patients with AIDS-KS with lesser CD4 counts and detectable HIV VLs. Twenty (22%) of the 91 patients had newly diagnosed, persistent or progressive KS despite CD4 counts >300 cells/mL and undetectable HIV VLs. Although tumor stage and response to KS therapy were similar, there was a significantly greater risk of death among the patients with CD4 counts <300 cells/mL and detectable HIV VLs ($P = .048$). The patients with the higher CD4 counts required systemic therapy to control their KS but were significantly less likely to die and demonstrated a trend toward better 15-year survival than patients having KS with lesser CD4 counts and detectable HIV VLs²⁹.

Another retrospective analysis looked at survival of KS when diagnosed as an AIDS defining illness (ADI). Median survival for the 130 patients in this analysis with KS as an ADI, was 20 months versus 9 months for KS subsequent to another ADI ($n = 75$, $P < 0.001$). Poorer survival following KS diagnosis was associated with a lower CD4 count

at diagnosis of KS ($P = 0.002$), as well as extensive cutaneous or visceral involvement at diagnosis ($P = 0.009$ and $P < 0.001$ respectively)³⁰.

Limitations in the two prior studies include that their analysis was related to overall survival and not specific survival of KS. Therefore the patients with lower CD4 levels were likely to be more immunocompromised and sicker overall, with a higher potential to succumb to illnesses other than KS. In such an instance, the CD4 level prognosticates, but not directly with KS outcomes.

A retrospective study of 5873 individuals with HIV-1 infection found 326 (6%) of these patients had a history of KS. In 262 (80%) of these KS patients, KS was their first ADI. Univariate and multivariate Cox regression analyses were performed to identify predictors of survival in this group. A prognostic index model was developed from this analysis. Increasing CD4 counts were found to have a significant positive effect upon survival, and used as a major point in their proposed prognostic index in AIDS patients diagnosed with KS³¹.

A large retrospective trial looked at prognosis in terms of relapse rate and mortality. Ninety-eight patients that had been treated with pegylated liposomal doxorubicin (PLD) were evaluated to assess tumor relapse rate, mortality, and cause of death in these subjects. A relapse study was performed for 61 patients who had complete or partial response to PLD and who attended a control visit after treatment completion. After a median follow-up of 50 months (interquartile range, 17.2-76 months), 8 patients (13%) had experienced relapse, 5 of which experienced relapse within the first year after stopping PLD. The only factor found to be independently related to risk of relapse was having a CD4 cell count < 200 cells/ μ L at baseline (HR, 6.2; 95% CI, 1.2-30). CD4 cell counts that were lower at the end of follow-up were also associated with relapse but to a lesser degree (HR for every increase in CD4 cell count of 100 cells/ μ L, 0.7; 95% CI, 0.6-1.01)³².

In 2003, the Italian Cooperative Group on AIDS and Tumors published a retrospective review of 211 patients with AIDS related KS. This is the one retrospective study that did not find prognostic information correlating with CD4 counts in AIDS patients diagnosed with KS. Their conclusions were that CD4 levels no longer provide prognostic information in their study in the era of HAART.

Other prognostic information and survival data in regards to ACTG classification was obtained from their data analysis; their 3-year survival rate was 83% for I0 patients and 71% for I1 patients ($P = .06$). For T0 patients this was found to be 83% and 69% for T1 patients ($P = .007$), and 83% for S0 patients and 63% for S1 patients ($P = .003$). In the multivariate analysis, only the combination of poor tumor stage (T1) and poor systemic disease (S1) risk identified patients with unfavorable prognosis. The 3-year survival rate of patients with T1S1 was 53%, which was significantly lower compared with the 3-year survival rates of patients with T0S0, T1S0, and T0S1, which were 88%,

80%, and 81%, respectively ($P = .0001$). Therefore while this study did identify good risk categories (T0S0, T1S0, T0S1) and a poor risk category (T1S1), it did not find prognostic information with CD4 counts or I at diagnosis of KS²⁷.

Overall the data supports CD4 levels to be correlated with various outcome measures and prognosis. CD4 levels studied include those at time of diagnosis, at follow-up and at relapse, all of which to some degree were found to predominantly correlate to outcome. While many of the specific treatment trials are not discussed in this chapter, the data presented here and in the literature is predominantly limited to retrospective studies. Additional prospective randomized controlled trials are necessary to further evaluate the CD4 levels and their correlation with prognosis.

What is the prognosis of KS treated with HAART?

One randomized controlled trial, but no systemic reviews of antiretroviral therapy as a systemic treatment for AIDS KS were found. A small prospective cohort and several retrospective studies were also identified.

For AIDS-KS the initiation of HAART improves overall survival. It is associated with an 80% reduction in death, prolongs the time to treatment failure, and prolongs survival of patients with pulmonary KS who also receive chemotherapy. It is still not entirely clear if, when, and what chemotherapy regimens should be used in addition to HAART, and for how long in advanced KS stages should HAART be continued. New prognostic indexes are being proposed based upon HAART therapy as the primary treatment in AIDS KS patients, with the addition of chemotherapy in more advanced disease stages. The development of a prognostic index model may help aid in the development of future prospective randomized controlled studies, which may help to further answer these questions regarding chemotherapy initiation.

One randomized controlled trial was found in the literature on this subject. It included moderate to severe KS patients who were failing HAART therapy or were HAART naïve. The patients were randomized to treatment with HAART therapy or HAART therapy with pegylated liposomal doxorubicin (PLD). The response rates in the HAART group were 20%, versus 76% in the HAART plus PLD group. While HAART clearly has a role in the treatment of AIDS and KS, these results indicate that in moderate and advanced KS, the addition of PLD is superior to HAART alone.

There are many systemic treatment modalities for KS, especially in advanced disease, but none of these other therapies have been compared in a randomized trial to HAART alone.

Using multivariable analysis, undetectable HHV-8 ($p = 0.009$) and relative variation of CD4 ($p = 0.005$) were

independently selected as having a predictive value for clinical response. KSHV=8 quantitative viral charge is an independent predictive factor of the efficacy of HAART on AIDS-KS. Their results support immune reconstitution as a mechanism of response of KS to HAART³³.

A prospective study on 254 consecutive patients was performed to evaluate the clinical outcomes of patients diagnosed with KS since the introduction of HAART. The median follow-up was 4 years and a maximum of 12 years. At KS diagnosis, only 19% of patients were on HAART. Seventy-nine (31%) patients had ACTG stage T1 disease at KS diagnosis, and 122 (48%) had CD4 cell count < 150 cells/ μ L. The overall 5-year survival was 89% (95% CI 84-93). One hundred and sixty-three patients were treated with HAART alone for T0 stage KS. One patient died of KS and 37 (22%) required chemotherapy, resulting in an overall survival at 5 years of 91% (95% CI 87-95) and a systemic treatment-free survival at 5 years of 74% (95% CI 67-82)³⁴. This study showed a good success rate of HAART in KS patients over a prolonged period of follow-up for KS with low staged disease.

This was the first randomized study to assess HAART on HIV-related KS survival. The other retrospective studies mentioned have demonstrated degrees of positive outcomes with HAART, but these were not randomized controlled trials, and many pertained to patients with low grade KS. The retrospective and limited prospective data indicate that HAART improves outcomes and survival in treatment of KS and has a definite role in the treatment of AIDS and KS. What is still not entirely clear is the role of HAART in improving outcomes in advanced disease and what role it has in the spectrum of treating KS. While many treatment studies have continued HAART AIDS therapy when treating advanced KS with other chemotherapeutics, it is unclear how much the HAART therapy affected KS survival in those advanced cases. The one study that compared HAART and chemotherapy versus chemotherapy alone did show increased survival benefit. Additional prospective studies are needed to better stratify this data since there are multiple limitations with this approach in critically evaluating long-term survival comparisons. Evidence-based data on specific chemotherapeutic regimens are discussed under the chapter regarding treatment of KS and are not covered in this chapter.

A prospective study evaluated the efficacy of HAART for KS in 22 HAART naïve patients who were treated at a single Italian HIV/AIDS referral center³⁵. Clinical, virological and immunologic responses to HAART were assessed. Peripheral blood mononuclear cell (PBMC)-associated HHV-8 viral load was also evaluated by PCR in 13 patients with clinically sustained complete response (CR). In a median follow-up of 40 months (range 17-78), the KS overall clinical response rate was 91%; 18 complete and 2 partial responses were achieved. For the complete sustained responders, a decrease in PBMC HHV-8 load was observed at CR, and a significant further reduction

was found at the end of follow-up. In this study, HAART naïve AIDS patients diagnosed with KS showed high clinical response rate of KS to HAART. These findings support HAART as a treatment modifier of KS in AIDS patients³⁵.

Multiple other studies have evaluated HAART in the treatment of KS. None of these were randomized controlled trials, but they do show evidence to support the important role of HAART in the treatment of KS.

A retrospective analysis was performed on 162 patients treated with HAART for stage T0 KS. Of the 162, 1 died of KS and 37 (22%) required additional chemotherapy for disease control, giving a systemic treatment-free survival at 5 years of 74% (95% CI 67-82) and the overall survival at 5 years is 91% (95% CI 87-95). While not a randomized controlled trial, these findings support HAART as an effective approach for treatment stage T0 Kaposi's sarcoma³⁴.

A retrospective analysis was performed using data from 387 HIV-infected men in the Multicenter AIDS Cohort Study who had been diagnosed with either KS non-Hodgkins lymphoma in the 1990s. Potential prognostic factors, including prior HAART treatment, were evaluated. Forty-three of 287 KS patients (15%) had been treated with HAART. HAART treatment was associated with improved survival (log-rank p = 0.0001). In multivariate analyses, HAART was associated with an 81% reduced risk of death among KS patients [relative hazard (RH) 0.19, 95% confidence limits (CL) (0.08, 0.45)], compared to those not exposed to HAART. Their conclusion was that HAART appears to be effective in improving survival in KS patients even in those who were HAART naïve prior to diagnosis³⁶.

A retrospective study performed on a cohort of 78 patients whom had received systemic or local treatment for AIDS-related Kaposi's sarcoma who subsequently commenced HAART, looked at the time to treatment failure for KS before and after starting HAART. Time to treatment failure was calculated from the end of last therapy to the start of the next new treatment for KS. Thirty-eight percent of patients were stage T0I0 at presentation. The median time to treatment failure before starting HAART was 0.5 years. The median follow-up after starting HAART was 12 months (range, 0.5-52 months) and anti-Kaposi's sarcoma treatment had been required for 24 (31%) patients. The median time to treatment failure for KS from the start of HAART was 1.7 years, which was a longer time to treatment failure for the same cohort of patients before they started HAART (log rank chi² = 16.5, P < 0.0001). Their conclusions were that HAART is associated with prolonged time to treatment failure in KS³⁷.

A retrospective cohort study on epidemiologic, clinical, and outcome data for 160 patients who were naïve to HAART at the time of KS diagnosis was compared with the corresponding data for 51 patients already receiving HAART at the time of KS diagnosis. The frequency of cutaneous involvement was similar in both groups, but cutaneous disease was more indolent among KS-HAART patients, with 1 anatomic site of involvement in 9 patients (21%)

and less than 10 lesions in 26 patients (60%), compared with 16 patients (12%; $P = 0.06$) and 47 patients (34%; $P = 0.01$), respectively, in the KS-naive group. The 3-year survival rates of KS-HAART patients (64%) and HAART-naive patients (78%) were not significantly different. They concluded that KS exhibits a less aggressive presentation in patients already receiving HAART compared with patients who are naive to HAART at KS diagnosis but outcome measures do not appear to be influenced by the initiation of HAART before development of KS²⁷.

A retrospective analysis of 48 AIDS patients with extensive KS who received chemotherapy from 1995 to 1999 was performed to evaluate differences in prognosis in those also receiving a protease inhibitor (PI)-based antiretroviral (ARV) therapy. All patients received at least one cycle of chemotherapy, including vincristine/bleomycin or an anthracycline-containing regimen. There was a significant difference in the median survival (MS) between the 28 patients (58%) treated with PI-based antiretroviral therapy (31 months [range, 1.8-48]) and the group not receiving PI (7 months [range, 1-28], $p = .0001$). In addition, 81% of patients in the PI group were alive at 18 months from initiation of chemotherapy versus 12% in the non-PI group. Death due to KS occurred in 6 of 28 (21%) patients (total 9 deaths) in the PI group and 14 of 20 (70%) patients (total 18 deaths) in the non-PI group ($p = .001$). Their results indicate that patients with advanced KS who received PI-based ARV therapy in addition to their chemotherapy treatment had improved survival, including KS survival, when compared to the group not treated with a PI²⁵.

A study evaluating survival with HAART in pulmonary KS retrospectively looked at 37 consecutive patients with pulmonary KS treated with chemotherapy. There were 16 patients not treated with HAART and 21 patients treated with HAART in their review. Kaplan-Meier analysis indicated that patients on HAART had substantially better survival ($P < .0001$). Cox multivariate analyses showed that HAART therapy was associated with a reduced risk of death (HR = 0.09; 95% CI, 0.03 to 0.69). They concluded that in patients with AIDS-associated PKS undergoing chemotherapy, administration of HAART was associated with increased survival³⁸.

Limitations with this study are that these groups were stratified by dates into the pre-HAART era and the post-HAART era. Those in the post-HAART era were likely to

have an independently improved survival since treatment and understanding of AIDS increased over time significantly in the 1990s, as did treatment for AIDS related KS.

Conclusions

KS is more frequent in immunosuppressed patients. Immune status and CD4 counts have been known to correlate with prognosis. The prognosis of KS has improved in AIDS patients in correlation with the advent of HAART. While HAART has a role in KS treatment, exactly what that role is and when to start, when to initiate other treatments independent of HAART, and when to stop HAART has been a subject of debate. The data indicates that HAART improves prognosis of KS with or without other treatments, and evidence supports continuation if possible while on other treatments as indicated.

See What We Know-KS

III. SQUAMOUS CELL CARCINOMA AND HUMAN PAPILLOMA VIRUS

Background

Human papilloma virus (HPV) has been demonstrated to be one etiologic agent associated with the development of squamous cell carcinomas, (SCC), especially of the anogenital and oropharyngeal mucocutaneous locations. HPV has been found to be present at high copy numbers, frequently integrated, and often transcriptionally active in these SCCs. There is a significantly higher incidence of HPV associated SCCs in immunosuppressed patients.

Perhaps the most well known, and possibly most studied of the SCC within this category, is the association of HPV and cervical cancer. In this section we will focus on SCC in external, non-cervical, mucocutaneous locations including those in non-cervical anogenital lesions, oropharyngeal, and other head and neck cancers. While HPV SCCs are certainly known to occur in other cutaneous sites, the vast majority of prognostic data on SCC induced in association with HPV currently exists in regard to cervical, anogenital, and head and neck cancers.

Based predominantly upon studies with HPV and cervical cancers, “high risk” HPV types have been defined. These include HPV types 16 and 18, which are the types most associated with 70% of cervical carcinomas. Over

What We Know: KS

- KS is a multi-focal vascular neoplasm that may regress in response to improvement in host immune function
- Prognosis, including disease free survival specific for KS, has been demonstrated to relate to CD4 count in AIDS-related KS.
- In randomized controlled trials HAART with the combination of chemotherapy in more extensive or advanced KS cases has been shown to improve survival compared to pegylated liposomal doxycy whole. Several other trials have shown improved survival, including KS disease free survival, with HAART.

expression of p16 is considered a surrogate marker for HPV infection, and has been looked at in some studies to evaluate for HPV status.

SEARCH METHODOLOGY

The Cochrane Library for systematic reviews (2009) and Pubmed/Medline (1976–September 2009) were searched for prognostic outcomes for HNSCC mesh terms HPV.

Additional searches were performed under the sub-category questions in regard to prognosis.

What are the prognostic outcomes of SCC of the oropharynx with HPV versus without HPV?

HPV infection has been associated with improved outcome in HNSCC, although not all the studies have shown consistent results. Based on the epidemiological evidence to date, hypotheses exist that HPV-positive and negative HNSCC represent different lineages formed through diverse, though overlapping, mechanisms of multi-stage tumor genesis. This is a not an uncommon relationship seen in viral oncogenesis.

A meta-analysis was performed evaluating OS and DFS in HNSCC. They found that patients with HPV-positive HNSCC had an improved outcomes compared to HPV-negative HNSCC. Specifically this was seen as a lower risk of dying (HR: 0.85, 95% CI: 0.7-1.0), and a lower risk of recurrence (HR: 0.62, 95%CI: 0.5-0.8) than HPV-negative HNSCC patients. Site-specific analyses show that patients with HPV-positive oropharyngeal tumors had a 28% reduced risk of death (HR: 0.72, 95%CI: 0.5-1.0) versus patients with HPV-negative oropharyngeal tumors. For DFS similar findings were obtained (HR: 0.51, 95% CI: 0.4-0.7). However for non-oropharyngeal tumors, this improvement in both survival measures was not seen, leading them to conclude that HPV-positive HNSCC tumors may have a distinct etiology from those tumors in non-oropharyngeal sites in this meta-analysis³⁹.

A large international randomized controlled phase III trial was performed on patients with previously untreated Stage III or IV head and neck squamous cell cancer who were randomized to receive >60 Gy definitive radiotherapy concurrently with either cisplatin or cisplatin plus tirapazamine. The prognostic importance of HPV in patients with oropharyngeal SCC (OPSCC) was evaluated in the analysis. Assays were obtained for HPV types 16/18 in 195 patients, for p16 in 186, and for both in 173 patients. Twenty-eight percent (54/195) were HPV positive, and this group was associated with better 2-year OS (94 vs. 77%, $p = 0.007$) and better failure-free survival (FFS) (86 v 75%, $p = 0.035$) compared to HPV negative tumors. After adjustment for clinical factors, including stage, the HPV positive group had better OS than the HPV negative group (HR

0.29, $p = 0.018$). Another finding in their analysis was that tumors with p16 expression fared better overall independently of tumor HPV status. This marker has been looked at in several studies and is discussed further under subsequent studies⁴⁰.

A prospective study evaluated outcome in HPV-16 negative HNSCC versus HPV-16 positive HNSCC when treated with surgical plus chemotherapy treatments and found that HPV-16 positive tumors had better outcomes in comparison to the HPV-16 negative group. Patients with resectable, untreated stage III or IV HNSCC of the oral cavity, oropharynx, hypopharynx or larynx, and stage II cancer of the base of tongue, hypopharynx and larynx were included. HPV-16 was detected by PCR in 14 of 24 cases. There was a trend toward better progression-free (HR=0.15, 95% CI=0.002-12.54; $p=0.06$) and OS (HR=0.14, 95% CI=0.001-14.12; $p=0.10$) for HPV-16 positive patients. There were however no significant differences in response rates (86% vs. 90%) in HPV-positive and HPV-negative patients, respectively.

HPV-16 has been demonstrated to be associated with a higher risk of cancer than other HPV strains in cervical and some anogenital infections. Despite its association with cancer, in this selected subgroup analysis, it fared a better prognosis than those tumors without HPV-16⁴¹.

Several other retrospective analyses have been performed evaluating HPV presence in various HNSCCs. Predominantly, these analyses have shown that HPV positive tumors are associated with a better outcome. Kong et al. demonstrated that a group showing strong HPV signal presence on molecular analysis fared significantly better than the group not demonstrating this HPV presence. Time to progression (TTP, $p = 0.008$) and overall survival (OS, $p = 0.004$) for all patients and for the oropharyngeal subset was seen in the HPV positive tumor group in their analysis⁴².

Despite studies that predominantly support HPV HNSCC as having improved prognostic outcomes, one retrospective study on 101 patients did not find differences in OS or DFS between HPV negative and positive SCC of the upper aerodigestive tract (UDAT). They found HPV DNA by PCR in 17 of 101 specimens. The HPV detection rate was similar for T1-T2 tumors (17.4%) and T3-T4 tumors (15.6%). While they did report that tumors without lymph node metastasis were more likely to be HPV positive (21.4%) than tumors that had metastatic lymph node involvement (6.5%), no overall differences in survival were found. These findings may have been in part due to the low detection rate of HPV or having tumors in the UDAT, with some outside the anatomical areas of other studies on HNSCC⁴³.

Many studies have shown that patients with HPV and p16 positive oropharyngeal squamous cell carcinoma (OPSCC) have a significantly better prognosis, which is hypothesized by some to be caused by increased radiosensitivity of these

tumors. A study by Fischer et al, analyzed p16 expression and prognosis of OPSCC treated by either radiotherapy (RT) or primary surgery of 365 HNSCC, which included 85 OPSCC. Patients with p16 positive OPSCC exhibited a significantly better overall survival than those with p16 negative tumors ($p = 0.007$). In a multivariate analysis, survival benefit of patients with p16 positive OPSCC was independent of clinicopathological parameters such as stage classification and treatment modality. Also of note, the improved prognosis of p16 positive OPSCC was found after both RT and surgery, indicating that the increased radiosensitivity of the p16/HPV positive tumors is unlikely to be the mechanism of improved prognosis⁴⁴.

A few other studies looked specifically at HPV-16 in relation to prognosis in HNSCC. One of these was a retrospective study, 111 cases of OPSCC were evaluated for OS and DFS in relation to molecular HPV presence. Specifically HPV16 E6 mRNA was positive in 73 (66%) of 111 samples. On multivariate analysis adjusted for age, stage, and treatment, positive E6 mRNA was the only independent predictor for superior OS; for DFS, p16 expression or HPV-16 status determined by either method was significant. They concluded that HPV-16 positivity is associated with improved OS and DFS⁴⁵.

Another retrospective analysis looked at 71 cases of HNSCCs for evidence of HPV-16/18. They found no clear relationship between expression of HPV-16 and prognosis⁴⁶.

The overall evidence supports that HPV-positive HNSCC has a significantly better survival advantage compared with patients who were HPV tumor negative. This data will undoubtedly spur future treatment trials, which will yield further data regarding HPV status in HNSCC and prognosis, and move our understanding forward of viral oncogenesis.

What is the prognosis of anogenital SCC associated with the presence of HPV DNA?

A lot of information exists regarding HPV types and prognosis in regards to the development of cervical cancer. Less evidence exists in regards to cutaneous anogenital cancers

and prognosis with HPV. In this review we have focused on non-cervical anogenital lesions for several reasons including that dermatologists are not routinely involved in the management and outcomes of cervical cancers.

Van de Nieuwenhof et al. looked at molecular and histological expression in 130 vulvar cancers. They found that vulvar cancers without HPV integrated DNA had a worse prognosis⁴⁷.

Another retrospective analysis evaluated 55 vulvar cancers for the presence of HPV DNA for type 6, type 16, and type 18. When adjustment factors were controlled for including lesion size, age, tumor grade, and nodal metastasis using the Cox proportional hazards model, only HPV status remained an independent positive prognostic factor in their analysis⁴⁸.

Guo et al. retrospectively evaluated the relationship between clinicopathological features and HPV types in 100 cases of female lower genital tract carcinoma. Their findings concluded that the prognosis in vulvar carcinoma was more related to the histologic type rather than HPV⁴⁹.

Indennimo et al. looked at 18 anal cancers for the presence of HPV DNA. Twelve of these were SCCs. In these tumors HPV types 31-33 and 16 were found. They also included 6 cloacogenic tumors of the anorectal junction in their analysis. There was no significant difference in the prognosis between HPV-positive patients and HPV-negative patients. These results may have been partly due to the inclusion of the cloacogenic tumors in their analysis which may have a different mechanism and prognosis than the anal SCCs⁵⁰.

Conclusion

In SCC of the oropharyngeal and non-cervical anogenital locations, presence of HPV supports an improved prognosis. In the case of head and neck cancers, meta-analyses and large prospective trial data support this finding. In the case of anogenital SCC, there is limited, retrospective data regarding the prognostic value of finding HPV DNA. Future studies may substantiate improved prognosis of HPV associated tumors in these anatomical locations and are necessary to improve our understanding of the etiopathogenesis specific to these SCCs and to improve management.

See What We Know-SCC with HPV infection

What We Know: SCC with HPV infection

- HPV is frequently associated with SCC of the anogenital and head and neck cancers.
- Those cancers of the head and neck have predominantly been found to have HPV type 16 on molecular analysis.
- The prognosis of SCC of the head and neck has good prospective randomized controlled and meta-analysis data demonstrating that those SCC of the head and

- neck with HPV, regardless of treatment modalities, have an improved prognosis as compared to those SCC without HPV presence.
- More limited data suggests that anogenital cancers, excluding cervical cancer, may also have improved prognosis of SCC with HPV found in the tumors. Future randomized controlled trials will help to better clarify this.

IV. CONCLUSION

Our understanding of viruses in relation to mucocutaneous tumors has greatly expanded over the last twenty years. Prognosis related to these cancers is dependent on the type of virus and cancer, as well as many other clinical factors. As our understanding of the role of the viruses in mucocutaneous oncogenesis continues to expand, so likely will our understanding of treatment and prognosis of these entities. In the case of malignancies in which data supports improved outcomes in the virus positive tumors, enormous opportunities exist for improving treatments very specific to these subsets of tumors.

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IV

Pharmaco- epidemiology



Principles of Pharmacoepidemiology

58

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Pharmacoepidemiology is the study of the use and the effects of drugs in large numbers of people. The term pharmacoepidemiology reflects its roots in pharmacology, the study of the effect of drugs, and epidemiology, the study of the distribution and determinants of disease in populations. In short, pharmacoepidemiology is the application of epidemiologic methodology to pharmacologic issues. Although pharmacoepidemiology arose out of a need to study adverse drug reactions (ADRs), the field has grown to encompass many other issues such as pharmacoeconomic analyses, quality of life (QoL) outcomes, and pharmacovigilance.¹

The basic idea of pharmacoepidemiology is to measure the use and effects of drugs in a population and to determine the frequency and distribution of drug use outcomes in that population. Pharmacoepidemiologists employ a variety of research methods in order to study drugs. A *cross-sectional* study provides a 'snapshot' of health and illness in the population. That is, a cross-sectional study determines the prevalence of disease at one point in time. A *case-control* study, on the other hand, is a retrospective analysis which compares subjects with the condition of interest (cases) to those without the disease (controls) with respect to a possible exposure. Alternatively in a *cohort* study, a population of disease-free individuals are followed over time and studied for the development of disease with respect to the exposure in question. A cohort study is the best way to determine incidence of disease in a population. Finally, the gold standard of research methods is the *randomized clinical trial* (RCT). A RCT is an experimental approach in which subjects are randomly assigned to a treatment group (typically an experimental therapy) and the outcomes are compared to that of a control group (placebo or standard therapy).²

PHARMAECONOMICS: ECONOMIC ANALYSES IN PHARMACOEPIDEMIOLOGY

As healthcare expenditures continue to grow in the face of increasingly limited funds, pharmacoeconomic studies are becoming particularly relevant to dermatologists. There are four fundamental types of pharmacoeconomic studies: cost analysis, cost-effectiveness analysis, cost-utility analysis,

and cost-benefit analysis. This chapter outlines the four types of studies (Table 58-1) and provides a framework for applying these studies as they relate to dermatology.

Cost Analysis

Cost analysis is the most basic form of pharmacoeconomic study. This type of analysis measures the cost associated with the treatment of a certain disease, irrespective of the outcome of the therapy. Researchers can derive costs from either microcosting or macrocosting. Microcosting involves enumerating each component of a therapeutic strategy and then determining the cost of each component.³ Cook et al. utilized microcosting methods to determine the true cost of treating a series of skin cancers with Mohs micrographic surgery and compared the costs to that of traditional methods of surgical excision. The authors systematically itemized the cost of treatment using Mohs micrographic surgery including diagnosis, surgery, reconstruction (if applicable), follow-up, and the cost to treat disease recurrence. The cost of Mohs surgery was then compared to the cost of diagnosis, excision, pathology, reconstruction, and disease recurrence using three traditional methods of surgical excision.⁴

Macrocosting determines the overall cost to care for a particular disease usually with a population-based approach. Emerson et al. utilized a macrocosting approach to evaluate the economic burden of atopic dermatitis in children aged 1-5 years in Nottingham, UK in 1995-1996. The estimation of disease costs included not only costs to the National Health Service for consultation and prescribing, but also the cost to families associated with changes to the home environment (e.g., mattress covers to reduce exposure to the house-dust mite), transportation to appointments, and loss of income for days taken off work as a direct result of the child's eczema.⁵

While cost analysis is useful as a source of enumerating costs and as the basis for other pharmacoeconomic studies, cost analyses do not account for outcomes and potential side effects. As such, the value of the therapeutic intervention cannot be easily measured. Even if a medication is costly, if it routinely improves lives it may have very high value.³

TABLE 58-1—Four Types of Pharmacoconomic Studies (Adapted from Ellis et al.¹ and Chen et al.²)

Type	Definition	Reported Results	Advantages/Disadvantages
Cost analysis	A determination of costs associated with an intervention with no consideration of outcomes	Sum of cost of medications, physician visits, and hospitalizations over a defined period of time	Does not account for side-effects, outcomes, or measure the value of a therapy
Cost-effectiveness analysis	A comparison of the cost per standardized unit of effectiveness for two or more interventions that provide varying outcomes	Cost-effectiveness ratio (Cost/Unit of clinical outcome)	Accounts for side-effects, outcomes, and value of a therapy Outcomes are not standardized across disease processes Results are not weighted according to importance
Cost-utility analysis	A comparison of the cost per quality-adjusted life year for two or more interventions	Cost-utility ratio (Cost/QALY)	Accounts for outcomes and value of a therapy Results are standardized and weighted according to importance Need to invoke some external criterion of value to interpret results
Cost-benefit analysis	A comparison of the costs and benefits of two or more interventions where outcomes are measured in dollars	Cost-benefit ratio (cost/benefit measured in dollars)	Accounts for outcomes and value of a therapy Do not need external criterion of value to interpret results Ethically difficult to assign a monetary amount to health

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Cost-Effectiveness Analysis

With the increasing presence of managed care, dermatologists will have to demonstrate that they can provide cost-effective care. Cost-effectiveness analysis (CEA) is one form of pharmacoeconomic analysis that can be helpful when decision-makers are confronted with a scenario in which an intervention is thought to be more effective but also more expensive than the currently available therapy.⁶ That is, CEA considers both the effectiveness of a health care intervention as well as the resources required to deliver the intervention.⁷ Unlike cost analysis where there is no attention devoted to the relative effectiveness of various therapies, in CEA, costs are related to a single common effect that may differ in magnitude between the alternative programs.⁸

In an incremental CEA, an old healthcare intervention is compared to a new intervention by a measure that compares the two: the difference in costs and outcomes between the old and new interventions. The alternative method may be some other treatment as long as there is a common effect. For example, psoriasis could be compared to seborrheic dermatitis if the common effect of interest is ‘years of clear skin,’ and these are independent programs (the cost and health effects in one patient group are not affected by the treatment alternative in any other patient group.)

A CEA in which the therapy in question is not compared to anything is termed an average CEA. This approach does

not provide useful information to the policymaker or clinician unless the currently available alternative therapy is to do nothing.⁷ However, if the standard of care is to “do nothing” and there are no associated costs and outcomes, then the average CEA is the same as the incremental CEA.

In quantifying the balance between costs and effectiveness, the cost-effectiveness ratio (CE ratio) is used to relate the extra costs required to achieve one extra unit of clinical outcome. The CE ratio is presented with costs in the numerator and health outcomes in the denominator. The CE ratio is a measure of value; the smaller the ratio, the fewer the resources required for a given unit of health outcome. The determination of costs in CEA is the same as discussed in cost analysis. The units of clinical outcome can be measured in direct clinical terms such as ‘years clear of psoriasis’ or ‘life years extended’.⁷

Once the CE ratio is determined for a particular intervention, how does one decide whether it should be adopted? In CEA, a cost-effectiveness threshold assists with this dilemma. The CE threshold is traditionally held at \$50,000 per quality adjusted life year (QALY). Interventions which cost less than this threshold, compared to standard therapy, would be considered cost-effective whereas interventions that cost much more than this threshold would not be considered cost-effective. This threshold is historically derived from the cost per QALY of providing dialysis, one of the first interventions thought to extend life years as well as improve QoL. At the time, the CE of dialysis was

\$35,000/QALY; adjusted for inflation, the threshold has risen to \$50,000/QALY.

Keogh-Brown *et al.* published a CEA comparing the cost-effectiveness of different treatments for cutaneous warts in the UK. The most common treatments for cutaneous warts, salicylic acid and cryotherapy, were compared to ‘spontaneous resolution’ (i.e., do nothing) and incremental cost-effectiveness ratios for each treatment were constructed.⁹

Though CEAs are useful measures of pharmacoeconomic analysis, they do have two main drawbacks. First, while CEA is useful for comparing a variety of therapies for a specific disease or within a field, the outcome measure is not standardized making comparison among different disciplines difficult. For instance, the outcome measure in a CEA studying a new therapy for psoriasis may be the ‘number of years of clear skin’. While this could be a common measure of effect when comparing psoriasis and seborrheic dermatitis, in most cases policy makers need to consider a multitude of therapies for a variety of different diseases in fields other than dermatology. It would be difficult to compare incremental CE ratios for new therapies in diabetes and onychomycosis if the outcomes measures were ‘mean HbA1c’ and ‘smooth nails,’ respectively.⁶

Second, CEA does not assign a weight to outcomes based on preferences of patients or society. At a time when health care funds are limited and policymakers are trying to stretch already constrained budgets, decision-makers are in need of a way to determine the relative importance of various outcomes in order to allocate limited resources.³

Cost-Utility Analysis

Cost-utility analyses (CUA) addresses the limitations of CEAs. While the determination of cost is the same as in CEA, the measure of outcome in CUA incorporates QALYs as the outcome measure such that results are expressed in terms of the cost per QALY gained by using one therapy versus another. In this way, CUA across different diseases can be measured.

The measure used to adjust life year in QALYs is derived from utilities. A ‘utility’ is a term used to reflect the preferences individuals or society may have for any particular set of health outcomes. As a preference-based metric, a utility is a numeric value that reflects ‘levels of subjective satisfaction, distress, or desirability that people associate with a particular health state’.¹⁰ These values are expressed on a continuous 0 to 1 scale with a utility= 0 being death and a utility=1 representing perfect health. Therefore, utilities closer to a value of ‘0’ indicate greater QoL burden compared to those values closer to ‘1’.

Thus, QALYS reflect both the additional quantity of life that a therapy extends and the quality of that additional amount of life. Mathematically, a QALY is calculated by multiplying life expectancy with a utility for that health state so that the length of life appropriately reflects the

decrease in QoL. By taking into account QoL through utilities, outcomes are not only standardized, but they are also weighted. CUA is particularly important in dermatology where many diseases and their therapies do not affect the length of life, but rather, QoL.

Pitt et al. published a CUA comparing pimecrolimus as a treatment for mild and moderate atopic eczema with conventional treatments such as topical corticosteroids and emollients. The authors utilized a condition specific QoL survey to estimate the utility of mild to moderate eczema in children. Costs were approximated by enumerating drug costs, quantity of treatment used, total area of body surface affected by eczema, and number of general practitioner and consultant visits. From this analysis, the authors concluded that there are likely to be few situations in which use of pimecrolimus for the treatment of atopic eczema could be justified on economic grounds.¹¹

Cost-Benefit Analysis

Unlike CEA and CUA, cost-benefit analysis (CBA) allows for comparison of health outcomes by assigning them a monetary value. Results are reported as differences between the costs and health benefits of a therapeutic program. The health benefits are represented in monetary terms, often by asking subjects how much they would be willing to pay for the therapy, although some CBAs are more indirect in their methodology. The ideal therapy is that which has the lowest cost per dollar of benefit. For instance, a study by Wootton *et al.* utilized CBA to compare real time teledermatology to conventional outpatient dermatologic care within the UK. The chosen measure of effectiveness was fewer number of additional primary and secondary care visits.¹²

The advantage of CBA is that by assigning a strictly monetary value to health outcomes there is a standard measure of comparing net benefits across diseases. In CBA, the decision to adopt a new therapy while foregoing an alternative therapy is strictly a monetary one. This is unlike CEA and CUA in which the investigator must utilize some measure of value, such as the CE threshold. In CBA, comparison of outcomes across diseases, whether it be disability days avoided or life-years gained, makes no difference.⁸

The task of assigning a generic measure of value to a health outcome is not easy. As such, one of the main criticisms of CBA lies in the moral and ethical nature of assigning a monetary value to human lives and QoL. However, proponents of this technique argue that translating health effects into monetary benefit is inherent in other pharmaco-economic studies, such as CEA/CUA where investigators must select a threshold below which a therapy is worth the cost. Another disadvantage of CBA lies in the ‘willingness to pay’ estimate of health benefits which is based on a patient’s conceptualization of how much they would be willing to pay for a therapy. In dermatology, however,

therapeutic options are often neither overly costly nor complex and thus it is reasonable to expect subjects to envision how much they would be willing to pay for a dermatologic therapy.³

In any pharmacoeconomic analysis, it is important to be clear about the perspective of the analysis as the perspective determines how costs and benefits are allocated. The three main perspectives in any pharmacoeconomic analysis are the individual patient, the third party payer, and society. If the perspective is that of the individual patient, then costs relate to co-pays and out-of-pocket expenses for a physician visit, medications, and time off from work needed to see the doctor. Conversely, third-party payers would be concerned about the cost of the medication and the physician visit, but not the co-pay or the time off from work. An analysis performed from the societal perspective would factor in costs that affect society as a whole: the cost of the medication and physician visit, loss of productivity from time off from work, and any impact on family members. The reader is encouraged to consult other references for a detailed explanation of standards in pharmacoeconomic analyses.¹³

QUALITY OF LIFE MEASUREMENTS AND THEIR APPLICATION TO PHARMACOEPIDEMIOLOGY

Health-related QoL, a patient's assessment of his or her QoL within the specific context of health, is an important component of pharmacoepidemiology. Drugs are not only studied for their ability to reduce mortality or prevent disease reoccurrence, but for their ability to improve a patient's subjective well-being as it relates to their health. This is particularly important within dermatology, where few cutaneous diseases are fatal, but nearly all diseases have the potential to significantly affect QoL.

There are a number of instruments available to assess QoL impact of disease. These instruments can be classified into two broad categories of health-related QoL instruments: health status surveys and preference-based measures. Health status surveys capture the impact of disease on various dimensions of QoL (e.g., physical, function, psychological, social aspects). These surveys can be generic measures that can be applied across a variety of medical conditions such as the Short Form 36 (SF-36) Health Survey. Dermatology-specific measures, such as the Dermatology Life Quality Index (DLQI) or the Skindex allow comparison of QoL among cutaneous diseases. Disease-specific measures such as the Psoriasis Disability Index (PDI) and RosaQoL measure QoL impact caused by psoriasis and rosacea, respectively. While generic health instruments allow for comparison of QoL among different diseases, they may not be sensitive enough to detect important aspects of QoL within a certain disease, nor are they usually as responsive to changes in health state as disease-specific measures. Conversely, disease-specific

instruments are not generic enough to compare QoL among different diseases.¹⁴

A Swedish study by Bingefors et al. sought to evaluate the impact of skin disease on QoL measured with the Short-Form-36 (SF-36), a multidimensional generic QoL instrument. As part of this study, the authors attempted to study differences in QoL by use of prescription and nonprescription dermatologic drugs. The authors found that a large segment of the population (20.5%) reported dermatologic problems and that skin disorders caused a significant decrease in QoL. Subjects using prescription topical dermatologic drugs generally scored lower (worse QoL) than other groups with cutaneous problems, reflecting the differences in severity and diagnoses among those reporting cutaneous problems.¹⁵

The preference-based QoL approach was discussed in the context of CUA above as utilities. Preference-based measures assess patients the desirability of life in a certain health state by having patients theoretically give up something of value (e.g., money, time, risk of death) in order not to have the disease in question. In this manner, the true burden of disease can be estimated.

The measurement of health-related QoL continues to gain significant attention in both clinical and research practice. Numerous studies indicate a substantial discordance between patient reporting and physician documentation of symptoms, as well as the degree to which physicians appreciate which symptoms patients find most burdensome.^{16,17} This discordance may affect quality of care, patient safety, and outcomes. Correctly estimating health-related QoL is not only important in clinical practice, but is garnering attention as an acceptable endpoint in randomized clinical trials as emphasis on patients' experiences and preferences has grown.¹⁸ The United States Food and Drug Administration (FDA) has noted that the measurement of QoL is more important than most other traditional measures used to assess efficacy (e.g., objective tumor response) in trials comparing treatments with similar or no impact on survival.¹⁹ Although more trialists are incorporating measurement of health-related QoL in their studies, the prevalence of reporting on QoL remains low.

A study by Sanders et al. examined the frequency and quality of reporting on QoL in randomized clinical trials from 1980-1997. The authors found that less than 5% of all randomized clinical trials reported on QoL. This proportion was below 10% even for cancer trials.¹⁸ One reason why relatively few randomized clinical trials measure QoL may be because of methodologic difficulties in determining what type of health-status measure to utilize and which measures have the most appropriate psychometric properties. While a disease-specific measure may be more responsive, certainly a more generic measure of QoL is critical in determining a global assessment of QoL. As initiatives are taken to develop standards for assessing and reporting QoL in clinical trials, it is hopeful that more trials will

incorporate endpoints based on a patient's determination of their own health status.

PHARMACOVIGILANCE

Pharmacovigilance, as defined by the World Health Organization (WHO), is the science and activities relating to the detection, assessment, understanding, and prevention of adverse effects or any other drug related problems.²⁰

The steps involved in pharmacovigilance begin with systematic data collection and management to determine possible drug safety hazards. Pharmaceutical companies are required by law to collect and submit all data relevant to the safety of their products both before and after licensing. Drug safety signals (a possible causal relationship between an adverse event and a drug) are also detected through spontaneous reports of suspected ADRs, primarily by healthcare professionals.²⁰ The number of ADR cases reported, however, may not be a good indicator of a signal as channeling of high-risk patients to newer therapies also leads to increased reporting with a newer agent. Nevertheless, when a signal of a suspected ADR arises from spontaneous reports, a case series should be constructed based on any previously reported cases. Although an analysis of the balance between benefit and risk is conducted throughout the life of a medicine, as data become available with each year on the market, regulatory bodies and companies may adjust their conclusions of benefit and risk. As such, regulatory action may be taken to increase benefit by improving use, reducing risk by improving communication about the drug, or restricting use altogether. Finally, an audit (evaluation) is conducted to determine the impact of the regulatory action.¹

The main outlets for pharmacovigilance in the United States include pharmaceutical manufacturers, academic/non-profit organizations, and the FDA. MedWatch is the FDA's voluntary reporting system for ADRs. Through MedWatch, healthcare professionals, patients, and consumers alike may report a serious adverse event, product quality problem, product use error, or therapeutic inequivalence and failure that is suspected to be associated with an FDA-regulated product (i.e., drug, biologic, medical device, dietary supplement, or cosmetic). The MedWatch system was created to maintain safety surveillance of these products. If a problem is detected, the FDA may modify use or design of the product, change its safety profile, or order product recalls and withdrawals. In addition, MedWatch disseminates important safety information in the form of medical safety alerts to both the medical community and the general public.²¹

One of the principal examples of pharmacovigilance within dermatology is the prescription of isotretinoin, a vitamin A derivative approved in 1982 for the treatment of cystic acne. Isotretinoin (trade name, Accutane) is a known teratogen when used during pregnancy because of the risk of spontaneous abortions and congenital malformations.

Since 1983, when isotretinoin was first documented as teratogenic in humans, the Dermatologic and Ophthalmic Drugs Advisory Committee of the FDA has issued restrictions on the prescription and dispensing of Accutane so that it may still be used as a treatment for cystic acne while minimizing the potential for fetal malformations.²² In response to the advent of generic isotretinoin compounds in 2002, the FDA launched iPLEDGE, a computer-based risk management program designed to further the public health goal of eliminating fetal exposure to isotretinoin. As of March 2006, physicians, patients, and pharmacists are required by the FDA to register and comply with the iPLEDGE program in order to use isotretinoin compounds.²³

SUMMARY

Pharmacoepidemiology is a diverse field, whose depth is beyond the scope of this chapter. Rather, this section serves to provide a framework for appreciating the basic principles of pharmacoepidemiology particularly as they relate to dermatology. Ensuring that patient care is delivered with an emphasis on minimizing costs and maximizing QoL impact with therapies that are deemed safe will continue to be a challenge for dermatologists and policy makers alike.

What We Know

- Pharmacoepidemiology is the study of the use and effects of drugs in large numbers of people.
- Pharmacoepidemiologists utilize cross-sectional, case-control, and cohort studies and randomized clinical trials in order to study drug outcomes in populations.
- Cost analysis, cost-effectiveness analysis, cost-utility analysis, and cost-benefit analysis are the four fundamental types of pharmaco-economic studies.
- Health-related quality of life is an important component of pharmacoepidemiology and can be assessed using health status surveys or preference-based measures.
- Pharmacovigilance occurs throughout the lifetime of a drug to identify potential adverse effects or any drug-related problems.

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Azathioprine

59

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INTRODUCTION

Azathioprine (AZA) is an antimetabolite drug that was developed in the late 1950s¹. It rapidly became a mainstay in post-transplantation immunosuppressive regimens². Currently, AZA is approved by the U.S. Food and Drug Administration for the treatment of rheumatoid arthritis and the prevention of renal transplant rejection; however, because of its favorable side effect profile relative to other immunosuppressive agents, AZA became widely used by dermatologists, rheumatologists, neurologists, and gastroenterologists for other “off-label” indications.

MECHANISMS OF ACTION

The exact mechanisms through which AZA exerts its immunosuppressive properties are not completely known. The active metabolites of AZA are 6-thioguanine nucleotides that act as purine analogues. They are incorporated into DNA, RNA, and some coenzymes preventing protein synthesis. Cell cycle arrest and apoptosis are triggered after incorporation of the purine analogues by a process involving the mismatch repair pathway³. Cytotoxicity is specific for the S-phase of the cell cycle⁴. Azathioprine also inhibits *de novo* purine biosynthesis through the actions of one of its metabolites, 6-methyl-thioinosine 5'-monophosphate (Figure 59-1). Consequently, rapidly dividing cells and cells lacking the purine salvage pathway (that therefore are dependent upon *de novo* purine) synthesis are those most affected by AZA. The function and proliferation of T-cells, B-cells, and antigen-presenting cells is reduced. Antibody production is reduced in B-cells, and there is decreased production of interleukin-2⁵. In the skin there is a reduction in Langerhans cells and other antigen-presenting cells⁶. Tiede et al. found that the AZA mediates T-cell apoptosis via the binding of its 6-thioguanine metabolite 6-Thio-GTP to Rac1 with consequent inhibition of CD-28-dependent Rac1 activation⁷. Blockade of Rac1 activation prevents the expression Rac1 target genes including mitogen-activated protein kinase, NF-κB, and bcl-xL, and leads to T-cell apoptosis via a mitochondrial pathway. Gene expression profiling studies in activated lymphocytes have demonstrated that AZA inhibits the expression of genes with prominent immunologic and inflammatory functions including TRAIL, 4-integrin, and TNFRSF7⁸.

PHARMACOKINETICS

Absorption

The oral bioavailability of AZA ranges from 27-83%, and the biologic half-life of the active metabolites is several hours^{4,9}. Steady state levels of the active metabolites of AZA are reached after 2-4 weeks of use⁴, and clinically, efficacy is usually apparent 8-12 weeks after treatment is started. The drug may be administered once daily or may be divided into two or three daily dosages. It may be given with food without interfering with levels of the active metabolites^{10,11}.

Metabolism and Excretion

AZA is a prodrug that must be converted into its active form (see Figure 59-1). The initial conversion of AZA to 6-mercaptopurine (6-MP) occurs via nonenzymatic attack by sulfhydryl-containing compounds such as glutathione or cysteine primarily in erythrocytes. Ninety percent of AZA is converted to 6-MP. 6-MP is then converted into active or inactive molecules by one of three competing enzyme pathways:¹ Hypoxanthine-guanine phosphoribosyltransferase (HPRT) converts 6-MP into 6-thioguanine metabolites that act as purine analogs, which are responsible for the immunosuppressive and cytotoxic properties of the drug.² Xanthine oxidase (XO) degrades 6-MP into inactive thiouric acid and is the enzyme responsible for the majority of the elimination of the drug.³ Thiopurine methyltransferase (TPMT) degrades 6-MP into inactive metabolites, and this is the main elimination pathway in hematopoietic cells. Inactivity, inhibition, or reduction in the amount of the two degradative enzymes, leads to an increase in the conversion of 6-MP by HPRT into active thioguanine nucleotides with a consequent increased risk of myelosuppression. Patients with high glutathione transferase activity are predisposed to adverse reactions to AZA therapy because of excessively high concentrations of free 6-MP and by depleting cellular glutathione¹².

Thiopurine Methyltransferase Genetic Polymorphism

Wide interindividual differences in the accumulation of thioguanine nucleotides occur after AZA administration. In the 1980s this was determined to be related to inherited

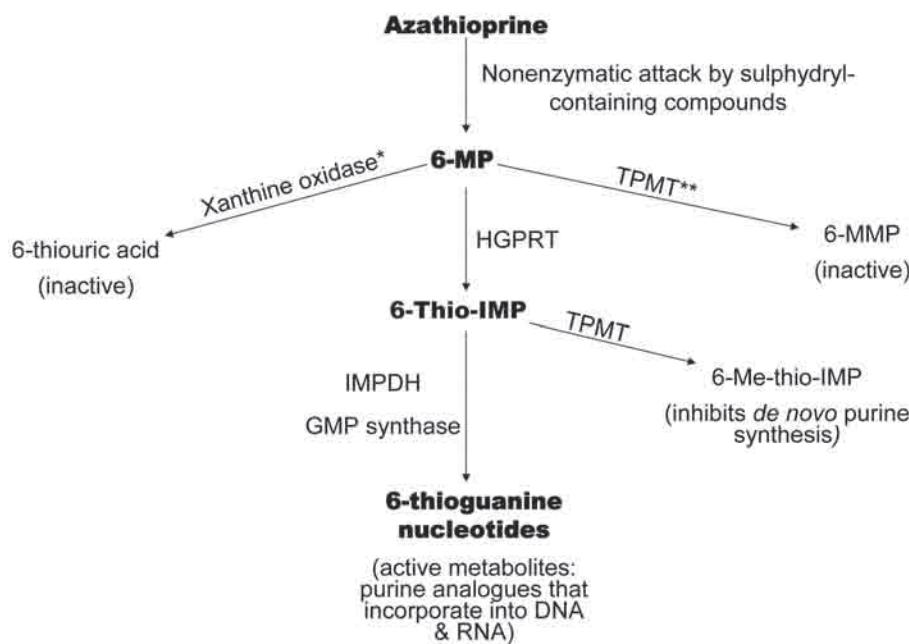


FIGURE 59-1 Metabolism of azathioprine. TPMT thiopurine methyltransferase, 6-MMP 6-methylmercaptopurine, HGPRT hypoxanthine-guanine phosphoribosyltransferase, 6-Thio-IMP 6-thiourine 5'-monophosphate, 6-Me-thio-IMP 6-methyl-thiourine 5'-monophosphate, IMPDH inosine monophosphate dehydrogenase, GMP synthase guanosine monophosphate synthase. *Main elimination pathway of azathioprine; inhibited by allopurinol. ** Main degradation pathway of azathioprine in hematopoietic cells.

differences in the activity of the TPMT enzyme¹³. The TPMT enzyme is encoded by a 27-kb gene on chromosome 6p22.3¹⁴, and 18 variant alleles have thus far been identified^{15,16}. Inheritance of alleles leading to normal TPMT activity is most common. Eighty to 95% of the intermediate and low activity TPMT phenotypes are caused by mutations in three alleles: *TPMT**2, *TPMT**3A—the most common variant alleles responsible for low TPMT activity in Caucasians^{17,18}, and *TPMT**3C, the most common variant allele identified in African, African American, and Southeast Asian populations^{18,19}. Although different alleles predominate among ethnic groups, some alleles have been reported in only one or a few individuals, suggesting that unique mutations may also be responsible for TPMT enzyme activity in some patients²⁰. In addition to the numerous TMPT variant alleles, variable-number tandem repeats in the promoter region of the TPMT gene that might be associated with differences in TPMT enzyme activity have also been identified⁴. Therefore, although genetic testing for common TPMT polymorphisms is widely available, genetic testing alone may miss a small number of patients with novel or rare mutations that affect TPMT.

Clinical Significance of the Azathioprine Metabolic Pathway

A high degree of concordance between TPMT genotype and phenotype (level of enzyme activity) has been demonstrated in Caucasians; patients whom are homozygous wild type have normal TPMT activity; those whom are heterozygous for mutant alleles often have intermediate enzyme activity, and those that are homozygous for mutant alleles have low or undetectable enzyme activity. This same high degree of genotype phenotype concordance has not been

observed in all other ethnic groups, and overall genotype-phenotype concordance rates of 57-99% in different populations have been reported^{19,21-25}. Because the concordance rates between genetic testing of TPMT mutations and phenotypic expression of TPMT activity are not high in all populations, baseline phenotypic testing is the more clinically useful tool for predicting patients at greatest risk of bone marrow suppression (those with low or undetectable TPMT activity). The TPMT enzyme activity level in erythrocytes correlates with that of all other cells, and therefore, the erythrocyte TMPT enzyme assay is a convenient means of assessing a patient's phenotype prior to initiating AZA therapy. This test should be performed in all patients prior to initiating AZA therapy to reduce the risk of drug-induced myelosuppression. It should be noted that exogenous factors such as recent blood transfusion might interfere with the interpretation of the TPMT activity assay.

There is a trimodal distribution of activity of the TPMT enzyme with approximately 90% of individuals having high activity, 10% having intermediate activity and 0.3% having low or no activity^{14,26}. Those found to have low or undetectable TPMT activity should not be treated with AZA because of the risk of fatal myelosuppression; those with intermediate TPMT activity level should initially receive dosages that are 30-50% of standard dosage. The majority of cases in which there is genotype-phenotype disparity are among those patients determined to have intermediate enzyme activity. When patients fail to respond to AZA at dosages prescribed based upon pretreatment TPMT activity, knowledge of their TPMT genotype may enable the physician to safely increase the dose (i.e., in a patient with intermediate baseline TPMT enzyme activity who is determined to actually have the wild type genotype), or seek an alternative therapeutic agent.

Recently, it has been shown that treatment with AZA may induce increased expression of the TPMT activity in some patients²⁷. Treatment with 5-aminosalicylic acid and uremia may also induce TPMT expression or increase its activity²⁸. Patients with immunobullous disease treated with AZA who experienced large inductions in TPMT were found to have disease that was resistant to AZA therapy²⁷. These patients had low levels of 6-thioguanine nucleotides, and elevated levels of 6-methylmercaptopurine (6-MMP), a metabolite that has been associated with hepatic damage in some patients when present in high levels^{29,30}.

Monitoring of 6-thioguanine levels and 6-MMP levels has been used to facilitate the safe use of AZA in several diseases. In patients receiving AZA for inflammatory bowel disease (IBD), the therapeutic effect has been found to have a better correlation with 6-thioguanine levels than with the absolute AZA dose^{28,31}. Specifically, 6-thioguanine concentrations greater than 235 pmol/8 X 10⁸ RBC are required for optimal efficacy in inflammatory bowel disease; however concentrations exceeding 400 pmol/8 X 10⁸ RBC have been associated with a high risk of myelosuppression^{31,32}. Similar studies have demonstrated that the optimum 6-thioguanine concentrations associated with therapeutic effect differ among diseases (Table 59-1). AZA metabolite monitoring has been studied in autoimmune hepatitis³³, leukemia³⁴, and solid organ transplantation³⁵, with different optimal therapeutic ranges of 6-thioguanine for each disease state found. In patients with systemic lupus erythematosus (SLE), 6-thioguanine levels of 159 pmol/8 X 10⁸ RBC were typical of patients benefiting from AZA therapy³⁶; however an earlier study failed to find a correlation between 6-thioguanine levels and outcomes of AZA therapy in patients with inflammatory diseases⁵. el-Azhary et al. evaluated 6-thioguanine concentrations in patients with immunobullous diseases and found mean optimum levels of 179.4 pmol/8 X 10⁸ RBC for pemphigus vulgaris and pemphigus foliaceus and 205.6 pmol/8 X 10⁸ RBC for patients with bullous pemphigoid²⁷. Patients with limited disease required lower concentrations than did those with generalized disease. These authors recommend assessing

the 6-thioguanine and 6-MMP concentrations in patients who fail to respond to AZA therapy. Low 6-thioguanine concentrations could indicate noncompliance or inadequate dosing (if 6-MMP concentrations are also low), or true refractoriness to AZA therapy (if 6-MMP levels are high, possibly mediated by induction of increased TPMT activity). It should be noted that the analytic method utilized can affect the results of 6-TGN monitoring assays with concentrations of 6-TGN varying up to 2.6-fold depending on the HPLC method used³⁷. While it may be helpful in determining the best course of action for a nonresponding patient, until adequately powered prospective studies confirm optimum metabolite concentrations for specific clinical indications, the measurement of AZA metabolites is not considered standard in the care of any dermatologic diseases. An approach to dosing AZA incorporating an understanding of its metabolism, and the effects of the TPMT genetic polymorphism is presented in Figure 59-1.

EFFICACY IN HUMAN STUDIES

Dermatologists have used AZA to treat a broad range of inflammatory dermatoses. It has been considered as a corticosteroid-sparing agent or alternative in almost any condition for which long-term immunosuppression might be warranted. The use of AZA for any dermatologic disease is off-label. Because dermatologists have used AZA since the 1970s, and its usefulness, especially in treating immunobullous and chronic eczematous diseases, was acknowledged before the advent of evidence-based medicine, the evidence to support its dermatologic uses is lacking in comparison to that of newer agents. Those dermatologic diseases for which AZA is most often used are discussed below.

Immunobullous Diseases

Corticosteroids remain the cornerstone for management of immunobullous diseases; however, steroid-sparing agents including AZA are widely used to aid in achieving disease control, to permit tapering of corticosteroids,

TABLE 59-1—Reported Disease-Specific Optimum 6-Thioguanine Concentrations

Disease	Optimum 6-TGN level (pmol/8X10 ⁸ RBCs)	Level of Evidence	Grade of Recommendation
Inflammatory bowel disease	235-400	II-3	C
Systemic lupus erythematosus	159	III	D
Pemphigus foliaceus & pemphigus vulgaris	179	III	D
Bullous pemphigoid	206	III	D
Renal transplantation	100-200	III	D

Adequately powered prospective studies confirming optimum metabolite concentrations for specific clinical indications are lacking; therefore, the measurement of AZA metabolites is not considered standard in the care of any dermatologic diseases. 6-TGN 6-thioguanine

and to maintain disease remission. In a 2007 review of interventions for the treatment of pemphigus vulgaris and pemphigus foliaceus from the Cochrane Database of Systematic Reviews, Martin, et al. determined that there is inconclusive evidence on the effects of AZA in treating pemphigus vulgaris. There is also inconclusive evidence regarding pemphigus foliaceus and remission, death, relapse, or withdrawal because of adverse events, and that no studies have yet adequately addressed the effect of AZA on time to disease control, severity score, antibody titer, or quality of life³⁸. Despite an overall lack of adequately powered, prospective, controlled trials, AZA is commonly used as a first-line steroid-sparing agent in immunobullous diseases³⁹⁻⁴⁵. AZA has been demonstrated to have a steroid-sparing effect⁴⁶, and a steroid-sparing effect superior to that of cyclophosphamide^{46,47} and mycophenolate mofetil⁴⁶. One study of 40 patients with pemphigus vulgaris found AZA to be less effective than mycophenolate mofetil in achieving disease control⁴⁷.

Cutaneous Lupus Erythematosus

The majority of patients with cutaneous lupus erythematosus (CLE), respond to standard therapies including photoprotection, topical, or intralesional corticosteroids, and antimalarial drugs. For patients with disease that is recalcitrant to these measures, second-line therapy with immunosuppressive or immunomodulating agents is required; however, there are no large, prospective, randomized controlled trials of any of these drugs in the treatment of CLE. Case reports and series have described the successful treatment of CLE with AZA. These reports have described the successful use of AZA for lesions of subacute CLE⁴⁸ and chronic CLE⁴⁸⁻⁵¹.

Dermatomyositis

There are many case series that report a steroid-sparing effect for azathioprine for muscle disease associated with dermatomyositis, but there is a relative paucity of reports about its usefulness for skin disease. Two papers appeared in the early 1980s based upon the same set of patients, first demonstrating a lack of steroid-sparing effect in a double-blind, placebo-controlled trial⁵² then in the open-label extension, demonstrating a corticosteroid-sparing effect⁵³. The probable reason for the initial study's lack of effect was that it was a 12-week study and the time to onset of effect is often just beginning at the time that this study was ended. It has been our experience that azathioprine has little effect on dermatomyositis skin lesions, but it continues to be used as a potential option as a third-line therapy.

Dermatitis

The use of AZA therapy for severe, refractory atopic dermatitis has been well described^{54,55}. In addition to case reports,

case series and retrospective studies, two randomized, double-blind, controlled trials of AZA therapy for atopic dermatitis have demonstrated significant improvement in atopic dermatitis severity, pruritus, and quality of life^{56,57}. Both of these trials included only adult patients; however, reports of AZA use in pediatric patients with severe recalcitrant atopic dermatitis suggest that it is a beneficial steroid-sparing agent in children⁵⁸⁻⁶⁰.

Chronic actinic dermatitis is treated with photoprotection, emollients, and topical corticosteroids. As in atopic dermatitis, brief intermittent courses of systemic corticosteroids may be needed for disease flares. For patients who require chronic systemic therapy, AZA is the first-line steroid-sparing drug⁶¹⁻⁶⁴. This recommendation is based on the results of two prospective controlled trials^{63,64}.

AZA has also been used to treat severe refractory pompholyx⁶⁵⁻⁶⁷ and severe chronic contact dermatitis⁶⁸⁻⁷⁴.

Neutrophilic Dermatoses – Pyoderma Gangrenosum and Behçet Disease

Neutrophilic dermatoses including pyoderma gangrenosum and Behçet disease⁷⁵⁻⁷⁷ have been treated with AZA. In pyoderma gangrenosum, corticosteroids (topical, intralesional, and/or oral) are typically utilized as first-line therapy. For those patients who fail to respond quickly to systemic corticosteroids, AZA may be of benefit; however, there have been no prospective, randomized-controlled trials to confirm its merits or lack thereof in the treatment of this disease. Results of case reports indicate that while some patients may improve with AZA⁷⁸⁻⁷⁹, others fail to respond^{80,81}. AZA should be considered only in patients with pyoderma gangrenosum who are refractory to or who will require prolonged courses of systemic corticosteroids. Although, it is a therapeutic option, we have most often used other agents, particularly the tumor necrosis factor alpha antagonists in the management of pyoderma gangrenosum, prior to considering AZA.

In addition to treating neutrophilic dermatoses, AZA has also been implicated as a potential causative agent in some patients with acute febrile neutrophilic dermatosis (Sweet syndrome)⁸²⁻⁸⁴.

Cutaneous Vasculitis

AZA has been used successfully in the treatment of many types of cutaneous and systemic vasculitis, including rheumatoid vasculitis⁸⁵, idiopathic leukocytoclastic vasculitis⁴⁹, polyarteritis nodosa⁸⁶, and Wegener's granulomatosis⁸⁷. Recent studies have shown that AZA is a safer and equally effective agent in maintaining remissions of ANCA-positive vasculitides in comparison to cyclophosphamide⁸⁷. In the treatment of purely cutaneous vasculitis, AZA should be reserved for treating severe disease.

Other Dermatoses

Reports of successful AZA use have been described for a number of other dermatoses including psoriasis^{88–90}, lichen planus^{91–96}, chronic erythema multiforme^{97,98}, chronic graft versus host disease^{99–100}, and polymorphous light eruption¹⁰². Alternatives that are safer, or for which there is better evidence, should be utilized before considering AZA in the treatment of these conditions.

SAFETY PROFILE

As an antimetabolite immunosuppressive agent, AZA use is associated with adverse effects including, myelosuppression/cytopenias, carcinogenesis, infection, and teratogenicity. Adverse gastrointestinal effects, hepatic effects, and idiosyncratic hypersensitivity reactions may also occur.

Myelosuppression/Cytopenias

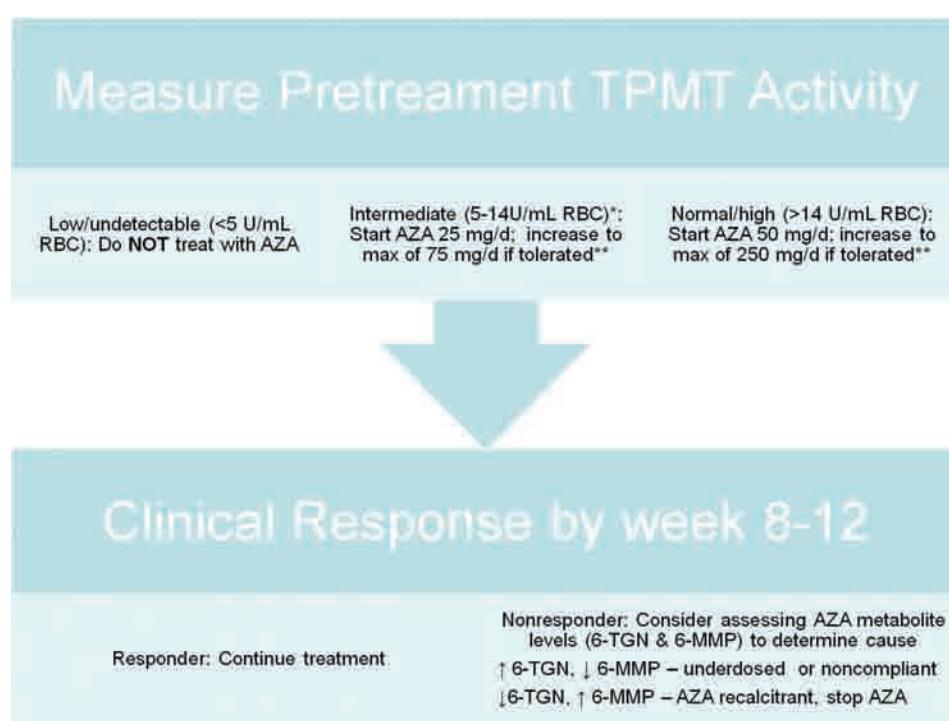
Myelosuppression and even more rarely, pancytopenia, may occur within weeks of initiating AZA or after years of use. It is therefore necessary to monitor complete blood counts at regular intervals throughout the duration of AZA therapy. Patients with low or absent TPMT activity (~0.3% of patients) will accumulate excessive levels of 6-thioguanine purine analogs that interfere with nucleic acid synthesis, especially in cells with high mitotic activity such as hematopoietic cells. These patients, therefore, are predictably at risk of acute myelosuppression after initiation AZA therapy and should not be treated with AZA (Figure 59-2). Abnormalities in other enzymes in the complex AZA metabolic pathway may be responsible for the cytopenias

that rarely occur in patients with intermediate or normal TPMT activity; consequently, complete blood count monitoring is still required for patients throughout the course of therapy regardless of TPMT status. Mutations in the inosine triphosphate pyrophosphatase gene have been found to be associated with increased cytotoxicity of AZA and with adverse events including thrombocytopenia, rashes, flu-like symptoms, and pancreatitis^{4,103–106}.

Carcinogenesis

Immunosuppressive agents have been associated with increased risk for carcinogenesis, and this risk is influenced by factors such as age, ethnicity, duration, and dosage of immunosuppression, and underlying disease state. There have been no significant studies evaluating the risk of carcinogenesis in patients taking AZA for dermatologic disease. An increased risk of malignancies, especially lymphoproliferative malignancies and cutaneous squamous cell carcinomas, has been reported in association with AZA use in select populations. Those whom appear to be at greater risk of developing malignancies in association with AZA therapy are organ transplant recipients and patients with rheumatoid arthritis.¹⁰⁷ Rates of malignancies have been evaluated in patients taking AZA for inflammatory bowel disease¹⁰⁸ SLE¹⁰⁹, and multiple sclerosis¹¹⁰, and an increased risk of carcinogenesis has not been demonstrated. However, there does appear to be an increased risk of hepatosplenic T-cell lymphoma, a rare peripheral T-cell lymphoma, in young patients who are treated concomitantly with AZA or prednisone and infliximab¹¹¹. This suggests that the risk of carcinogenesis may be linked to iatrogenic immunosuppression from any agent in certain

FIGURE 59-2 Dosing strategy for azathioprine. Doses are based on a 70 kg patient. *TPMT* thiopurine methyltransferase, *AZA* azathioprine, *6-TGN* 6-thioguanine, *6-MMP* 6-methylmercaptopurine. *An assessment of TPMT genotype by PCR should be considered for patients at the upper range of intermediate TPMT activity since some will be homozygous for the wild type (normal activity level) genotype and may be underdosed if treated based on TPMT activity assay alone. **The initial dose can be increased within 1–2 weeks and rapidly increased thereafter although gastrointestinal symptoms or abnormalities in laboratory monitoring studies may prevent dose escalation.



predisposed populations rather than to AZA specifically. Nonetheless, AZA has been found to be carcinogenic and mutagenic in animal and *in vitro* studies utilizing supratherapeutic doses of AZA¹¹², and conflicting studies in human subjects continue to raise concern for the risk of malignancy associated with this drug. Patients should receive counseling regarding the potential risk for systemic malignancy prior to beginning AZA therapy.

Patients with a history of marked sun exposure and long-term AZA therapy may be at greater risk of aggressive cutaneous squamous cell carcinomas¹¹³. AZA use in organ transplant recipients has been associated with a higher incidence of cutaneous squamous cell carcinomas than have other immunosuppressive drugs^{114,115}. *In vitro* studies have demonstrated that cells treated with the active metabolite of AZA (6-thioguanine), and UVA generate reactive oxygen species that could be responsible for the development of nonmelanoma skin cancers¹¹⁶. Although an increased risk of cutaneous squamous cell carcinomas has not been reported among patients with other underlying disease states, it seems prudent that the dermatologist closely follow patients receiving AZA for the development of cutaneous malignancies.

Infection

Patients taking AZA are at increased risk of infection. This risk is greater in patients taking higher dosages and in those taking additional immunosuppressive drugs. Patients who are immunosuppressed should not be given live attenuated vaccines because of the potential risk of atypical responses. Diminished cell-mediated immune responses to influenza vaccines have been demonstrated in organ transplant recipients receiving AZA¹¹⁷ (as well as in those on alternative immunosuppressive regimens), although humoral responses were similar to those of healthy controls¹¹⁸. In patients with SLE receiving AZA therapy, cell-mediated¹¹⁹ and humoral responses¹²⁰ to influenza vaccination were also reduced; although it should be noted that reduced humoral responses to vaccines is common in SLE regardless of treatment. Inactivated viral vaccines are safe in patients receiving AZA and should be administered when routinely indicated.

Gastrointestinal

The most common adverse effects of AZA are gastrointestinal, particularly nausea, vomiting, and diarrhea, and symptoms are worst in the first 1-2 weeks of therapy¹⁰⁷. These symptoms can often be relieved by dividing or reducing the dose and by administering it with food. Drug-induced pancreatitis has been reported with AZA; although the mechanism is not known, an association between mutations in the inosine triphosphate pyrophosphatase gene and AZA-induced pancreatitis was found in one study¹⁰⁴.

Hepatic

Hepatic dysfunction is a risk of AZA therapy. Hepatotoxicity has been associated with high concentrations of 6-methylmercaptopurine (6-MMPR)^{29,30}, the inactive metabolite generated by degradation of 6-MP by TPMT (see Figure 59-1). The measurement of 6-MMPR, however, lacks sensitivity and specificity to detect AZA-induced hepatotoxicity, and serial measurement of aminotransferases throughout the course of AZA therapy remains the most effective means of detecting liver damage. Hepatic dysfunction typically improves with AZA discontinuation, dose reduction, or dose division.

Hypersensitivity

Hypersensitivity reactions are idiosyncratic systemic drug reactions characterized by fever, flu-like symptoms, rashes, and leukocytosis (often with marked eosinophilia), and involvement of multiple organ systems including, but not limited to, the gastrointestinal tract, liver, kidneys, lungs, and cardiovascular systems. These reactions usually arise within the first 1-4 weeks of therapy and can be life threatening. Hypersensitivity reactions have occurred with AZA therapy^{121,122}.

Pregnancy and Lactation

AZA is classified by the U.S. Food and Drug Administration as pregnancy category D. AZA and 6-MP cross the placenta. The placenta strongly impedes their diffusion to the fetus; placental concentrations of AZA are 64-93% of that of maternal blood levels, and fetal blood concentrations of AZA and 6-MP are 1-5% and 1-2% of maternal blood levels of respectively¹²³. A number of studies have suggested that fetal risk may be more closely related to the mother's underlying disease rather than to effects of the drug itself^{124,125}. The most common pregnancy related risks include spontaneous abortion, growth restriction/low birth weight, and prematurity¹²³⁻¹²⁵. A slight increase in the risk of congenital malformations has been reported (0-11%), though there appears to be no consistent pattern of defects¹²³. Although there have been case reports of neonates with immunologic or hematologic dysfunction following *in utero* AZA exposure¹²⁶, overall, there does not appear to be a higher than expected rate of immunologic dysfunction amongst newborns with antenatal AZA exposure^{123,127}.

The safety of AZA in lactating women for whom the drug is deemed necessary has been suggested by studies demonstrating very low or undetectable, levels of 6-MP in breast milk^{128,130}, and undetectable levels of 6-thioguanine nucleotides in breast milk¹³¹. One study has suggested that infants ingest <0.008 mg/kg/24 hour of mercaptopurine from breast milk¹³². Although exposure to active metabolites of AZA to nursing infants appears to be minimal, long-term and large-scale studies demonstrating safety are lacking.

Drug Interactions

There are several important AZA-drug interactions including those with allopurinol, warfarin, angiotensin-converting enzyme inhibitors, sulfasalazine, and trimethoprim-sulfamethoxazole. Allopurinol inhibits xanthine oxidase, by blocking one of the inactivation pathways of AZA metabolism and causing elevated concentrations of the active metabolites. Patients taking both drugs are at increased risk for myelosuppression, and if a patient requires both, the AZA dose should be reduced by two thirds¹³³. The anticoagulant effects of warfarin are reduced by AZA, and patients frequently require 3-4 times the amount of warfarin to achieve appropriate anticoagulation^{134,135}. Sulfasalazine, trimethoprim-sulfamethoxazole, and angiotensin-converting enzyme inhibitors^{107,136} may increase the risk of myelosuppression when taken with AZA.

Monitoring

Monitoring recommendations based on a number of studies and expert recommendations^{27,107,137,138} are summarized in Figure 59-3.

CONCLUSION

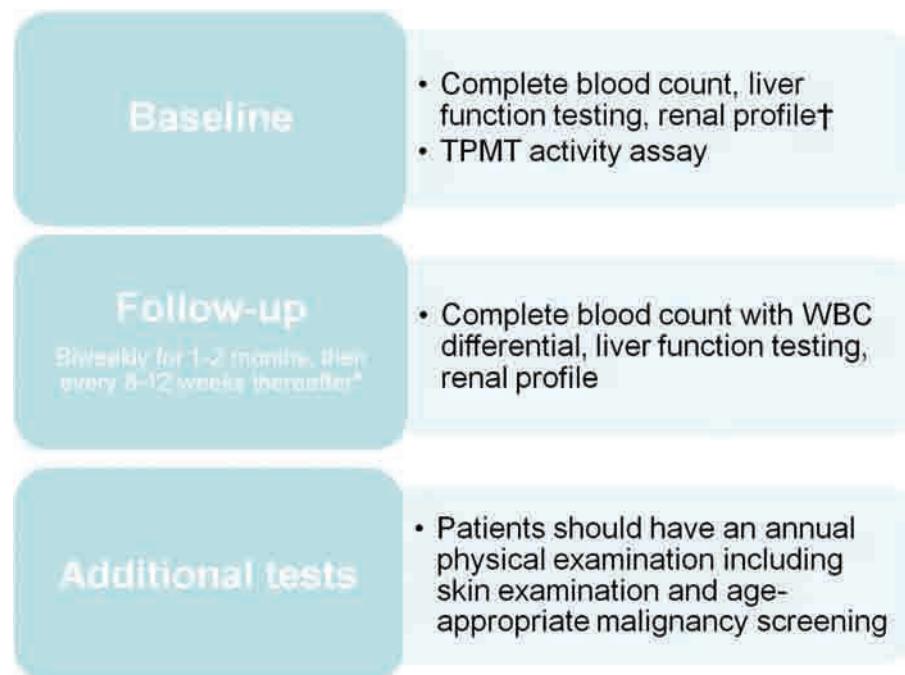
For more than 40 years, AZA has been used by dermatologists to treat severe inflammatory and immunobullous disease, and it remains commonly used despite the development of newer immunosuppressive drugs. The observation of the wide interindividual differences in accumulation of the drug and subsequent myelosuppression

What We Know

- Azathioprine is a prodrug of 6-mercaptopurine that is metabolized by 3 competing pathways. The active metabolite, 6-thioguanine, is a purine analog that is incorporated into DNA and RNA. T-cells, B-cells, and natural killer cells are preferentially affected.
- There is a trimodal distribution in the activity of the TPMT enzyme that is caused by a genetic polymorphism in the TPMT gene. Most patients (~90%) have high levels of TPMT activity; few (~10%) have intermediate activity, and even fewer (~0.3%) have low to undetectable activity. Patients with low TPMT activity accumulate higher levels of active metabolites and are at risk for life-threatening myelosuppression. All patients should undergo baseline evaluation of TPMT status prior to starting azathioprine, and the dose should be altered accordingly.
- Azathioprine is used (off-label) for a wide range of severe dermatoses, especially immunobullous diseases, refractory atopic and chronic actinic dermatitis, vasculitis, and autoimmune connective tissue diseases.
- Adverse effects of azathioprine include: myelosuppression, infections, carcinogenesis, hypersensitivity syndrome, hepatotoxicity, and gastrointestinal problems.
- Drug interactions include: ACE inhibitors, allopurinol, folate antagonists, and warfarin.

led to the discovery of the TPMT genetic polymorphism. The routine use of pretreatment testing of a patient's TPMT status to prevent toxicity made AZA a pioneering agent in the practice of pharmacogenomics. Refinements in our

FIGURE 59-3 Azathioprine monitoring guidelines. *TPMT* thiopurine methyltransferase. [†]If GFR <10 mL/min reduce dose by 50%; If GFR 10–50mL/min reduce dose by 25%. *When a dose increase is made, the monitoring should again be performed at biweekly intervals for 1-2 months and then resumed at every 8-12 weeks thereafter.



understanding of the complex metabolism of AZA and the genetic basis for varying responses to it, continue to shape clinical practice and pave the way for optimizing its safety and efficacy.

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Imiquimod

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INTRODUCTION

Imiquimod (IM) is a synthetic toll-like receptor 7 agonist that induces the expression of many proinflammatory cytokines. IM increases the host's innate and acquired immune responses against cutaneous infections and skin cancer. IM 5% cream is a home-based patient-applied treatment approved by the U.S. Food and Drug Administration (FDA) for external anogenital warts (AGW), superficial basal cell carcinoma (sBCC), and actinic keratosis (AK). Moreover, randomized-controlled trials (RCT) support the efficacy of IM for AGW and AK in immunocompromised patients, cutaneous leishmaniasis, nodular BCC, Bowen's disease, anogenital intraepithelial neoplasia and prevention of recurrence of shaved keloids.

MECHANISM OF ACTION

Our knowledge about the mode of action of IM has greatly increased in the past few years, and the mechanism of action is complex and appears to comprise several complementary components.¹ IM is a nucleoside analog without nucleoside-like activity that activates the immune response stimulating the toll-like receptor (TLR) 7. TLR7 is indispensable for host defense against viral infection by recognizing pathogen-associated molecular patterns (e.g. virus-derived single-stranded RNA) and IM is a potent TLR 7 agonist.² TLR7 is localized to the intracellular endosomal membranes of several immune cells. IM binds to TLR7 of macrophages/monocytes, dermal dendritic cells and plasmacytoid dendritic cells (PDC). IM induces a massive recruitment and activation of circulating PDC from the blood into the treated skin, and PDC are the main producers of cytokines after IM topical application.³ The TLR7 signaling pathway translocates nuclear factor-kappa B into the nucleus and activates the transcription of many immunomodulatory genes. The vast majority of the stimulated genes portray immunologic functions predominantly involving the activation of cellular innate and adaptive immune-effector mechanisms.

Interferon alpha (IFN- α) is the main cytokine induced by IM, but many other cytokines and chemokines are induced: IFN- β , tumor necrosis factor-alpha (TNF- α), interleukin (IL) 1 α , IL-1 β , IL-1 receptor antagonist, IL-6, IL-8, IL-10, IL-12, granulocyte-macrophage colony

stimulating factor (CSF), granulocyte CSF, macrophage/monocyte chemotactic protein 1 (CCL2) and macrophage inflammatory proteins 1 α (CCL3) and 1 β (CCL4).⁴ The cytokine induction by IM is dose-dependent, as early as 1 to 4h after stimulation with IM in human peripheral blood mononuclear cells, and the maximum peak production 8 hours occurs after topical application.⁵ Most of these cytokines and chemokines display proinflammatory activity and promote T helper cell type 1 adaptative immune responses. Moreover, IM also inhibits the production of IL-4 and IL-5, thus suppressing the development of a T helper cell type 2 adaptative immune responses.⁶

IM enhances the functional maturation of Langerhans cells (LC), bone marrow-derived epidermal dendritic cells that represent the major antigen-presenting cells in the skin. Activated LC takes up, processes local antigens within the skin, and migrates to the draining regional lymph nodes.⁷ Within the nodes, LC present processed antigens to naive CD4 T lymphocytes using MHC class II molecules. As a result, T lymphocytes develop clonal expansion and differentiate to memory and activated T cells that return to the skin, where they express T helper cell type 1 cytokines (INF- α , INF- γ and TNF- α).

IM rapidly increases the dermal inflammatory infiltrate, with a significant number of CD4+ T helper cells mixed with activated dendritic cells, CD8+ T cells, CD68+ macrophages, CD20+ B lymphocytes and PDC (CD 123+).⁸ Most CD8+ T cells express cytotoxic granules, T-cell restricted intracellular antigen 1, granzyme B and perforin. Furthermore, IM is a potent activator of B-lymphocytes, augments immunoglobulin production, up-regulates opioid growth factor receptor protein and suppresses the adenosine receptor signaling.^{9,10}

Apoptosis, also known as programmed cell death or cellular suicide, is a basic physiologic cellular process by which nonviable cells are eliminated. Apoptosis is a strictly regulated process, and many genes and proteins participate in its control. The main pro-apoptotic pathways are the membrane-bound death receptors (Fas, TRAIL and TNF receptors), P53, Bax and the activated cytotoxic cells, through the release of granules of granzyme B. The main anti-apoptotic protein is the Bcl-2, which interferes with Bax in the mitochondria. In vitro, IM induces apoptosis in melanoma, squamous cell carcinoma, human epithelial (HeLa S3) and human keratinocyte cell lines (HaCaT).

Moreover, IM activates several caspases and the Bcl-2-dependent cytosolic translocation of cytochrome c independently of the death receptors.¹¹ In vivo, IM increases apoptosis in melanoma and BCC, downregulates Bcl-2 expression in BCC,¹² and induces expression of Fas in BCC.

Finally, IM has demonstrated antiangiogenic activity. This effect appears to be mediated by IL-18, probably through promoting the production of INF- γ , the most important inhibitor of tumor cell-induced angiogenesis.¹³

PHARMACOKINETICS

IM is the lead compound of the synthetic imidazoquinolone family of drugs. The chemical formulation of IM is 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine (C14H16N4), and has a molecular weight of 240.3 Daltons (Figure 60-1). IM is a crystalline, odorless solid that varies from white to off-white in color. It is a stable compound, hardly soluble in aqueous systems and most organic solvents. IM sublimes at a melting point of 297°C to 299°C. The constant ionization for IM is about 7.5.

IM 5% cream is marketed in 12 sachet boxes (AldaraTM), manufactured by 3M Health Care Limited and distributed by Graceway Pharmaceuticals Inc (USA), MEDA AB (Europe) and iNova Pharmaceuticals (South Africa, Asia-Pacific region). The cream is packaged in single-use sachets containing 250 mg of cream and 12.5 mg of IM. Each gram of the cream contains 50 mg of IM in an off-white oil-in-water vanishing cream base consisting of isotearic acid, cetyl alcohol, stearyl alcohol, white petrolatum, polysorbate 60, sorbitan monostearate, glycerin, xanthan gum, purified water, benzyl alcohol, methylparaben, and propylparaben.¹⁴

IM 5% cream is a patient-applied therapy for external use only (Table 60-1). Before applying the cream, the

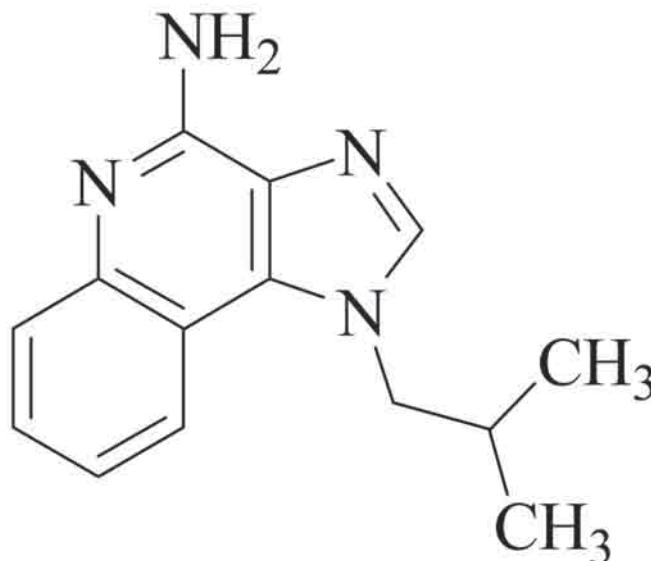


FIGURE 60-1 Imiquimod 1-(2-methylpropyl)-1*H*-imidazo[4,5-*c*]quinolin-4-amine, C14H16N4, 240.3 Da.

patient should clean the treatment area and dry it thoroughly. Enough cream should be applied to cover the treatment area, including one centimeter of surrounding skin. The contents of a sachet may be applied to a skin area of up to 386 square cm.¹⁵ The cream should be rubbed into the treatment area until absorbed (i.e., the cream is no longer visible), and the treatment area should not be bandaged or otherwise covered or wrapped to be occlusive. IM is applied before normal sleeping hours and left on the skin for 8 hours. After the treatment period, the cream should be removed by cleaning the treated area with mild soap and water. Minimal systemic absorption of IM through intact skin occurs during treatment with topical IM. Systemic drug levels were very low after single and multiple doses of IM in children aged 2-12 years.¹⁶

ANIMAL MODELS

The safety of IM has been studied extensively in mice. No treatment-related tumors were noted in an oral rat carcinogenicity study. IM revealed a statistically significant increase in the incidence of liver adenomas and carcinomas in a dermal mouse carcinogenicity study. The vehicle cream of AldaraTM decreased the median time to onset of skin tumor formation in a dermal photoco-carcinogenicity study with hairless mice, and no additional effect on tumor development beyond the vehicle effect was noted with the addition of the active ingredient. IM revealed no evidence of mutagenic or clastogenic potential based on the results of three in vivo genotoxicity tests (rat and hamster bone marrow cytogenetics assay and a mouse dominant lethal test). Daily oral administration of IM to rats, throughout mating, gestation, parturition and lactation, demonstrated no effects on growth, fertility or reproduction.¹⁴

The mechanism of action of IM has also been studied in mice. The murine dermal mast cells activated by IM were essential to initiate an early inflammatory reaction. Activated mast cells expressed TNF- α and IL-1 β and were able to promote the migration of LC in mice.¹⁷ Using a mouse hemangioendothelioma model, IM was found to be a strong inhibitor of tumor cell-induced angiogenesis.¹⁸ IM-treated tumors showed decreased tumor cell proliferation, increased tumor apoptosis, and increased expression of tissue inhibitor of matrix metalloproteinase-1 with decreased activity of matrix metalloproteinase-9.

EFFICACY IN HUMAN STUDIES

External Genital Warts

Anogenital warts (AGW, condyloma acuminata) are common highly contagious benign epithelial lesions occurring on the genitals, perianal area, and inguinal folds. AGW are one of the most common sexually transmitted diseases and are caused by human papillomavirus (HPV), with HPV 6 and 11 causing 90% of cases. Multiple therapeutic

TABLE 60-1—Clinical Applications of Imiquimod 5% Cream

RCT: randomized-controlled trials. Reference in brackets
Licensed indications with meta-analysis of RCT
External anogenital warts (20,21)
Superficial basal cell carcinoma (29)
Actinic keratosis (42)
Unlicensed indications with meta-analysis of RCT
Nodular basal cell carcinoma (29)
Unlicensed indications with RCT
External anogenital in HIV-positive patients (23)
Cutaneous leishmaniasis in combination with parenteral pentavalent antimony (27)
Bowen's disease (49)
Anogenital intraepithelial neoplasia (51)
AK and skin dysplasia in transplant recipients (47,48)
Prevention of recurrence of shaved keloids (56)

options are available for AGW. IM is one of five therapies equally recommended by the CDC for AGW. Standard therapies are invasive, ablative, caustic, painful and treat only the visibly appearing AGW, thus, recurrences are frequent. IM is approved by the FDA for the treatment of external AGW in individuals aged 12 years and over.¹⁹ IM is applied 3 times per week until total clearance or a maximum of 16 weeks. The once-daily regimen does not improve treatment efficacy but results in greater incidence and severity of local skin reactions.²⁰ IM is more effective for women and uncircumcised men than circumcised men. A meta-analysis of IM and 0.5% podophyllotoxin in the treatment of AGW revealed that the clinical cure rates of IM and podophyllotoxin were 50% and 56%, respectively, but podophyllotoxin had more serious adverse effects.²¹ IM is also associated with lower treatment-associated morbidity and lower recurrence rates when compared to conventional ablative methods.²²

The effect of IM on innate and cell-mediated immunity highlighted the possibility of using IM for viral skin infections in immunocompromised patients, and a RCT demonstrated IM efficacy for AGW in HIV-infected patients.²³

Other Viral Diseases

Although the use of IM for managing other skin infections has not yet been approved, there is a growing body of evidence supporting the efficacy of IM in the treatment of other HPV-related diseases such as common warts, subungual and periungual warts, plantar warts, flat warts, lip papillomatosis and epidermodysplasia verruciformis, even in immunocompromised patients.

Molluscum contagiosum (MC) is a skin infection caused by a poxvirus that causes small, firm, umbilicated papules. No consensus has been established concerning

the management of this condition. In-office therapies are very efficacious but they must be performed with adequate anesthesia and are time-consuming procedures. A small RCT demonstrated that IM was well tolerated and with high clearance rates in children with MC.²⁴ However, two RCT involving 702 children aged 2–12 years failed to demonstrate efficacy of IM for MC.¹⁴ Case reports suggest IM efficacy for MC in HIV-infected patients.

Although there are case reports of herpes simplex virus infections successfully treated with IM, it is not recommended in patients with recurrent disease. A pilot study with subjects with recurrent herpes labialis was terminated early because of severe local adverse events that occurred in recipients of IM.²⁵ Moreover, a RCT failed to show an effect on the short-term natural history of herpes genitalis recurrences.²⁶

Human orf or ectyma contagiosum is a self-limiting zoonosis caused by a parapox virus. Case reports suggest that IM is a safe and effective treatment for human orf infection.

Cutaneous Leishmaniasis

Cutaneous leishmaniasis is a serious public health problem in the developing world. Current treatments for this disease are limited by their toxicity, high cost, discomfort and drug resistance. New world cutaneous leishmaniasis has been treated with IM with some success. The combination therapy with topical IM and intravenous meglumine antimonate was well tolerated, accelerated healing of lesions, and improved scar quality in Peru.²⁷ However, a RCT showed no beneficial effect of combining IM and a standard course of treatment with parenteral pentavalent antimony in Iran.²⁸

Superficial Basal Cell Carcinoma

Basal cell carcinoma is the most prevalent malignant skin tumor in whites, and its incidence continues to rise. BCC is a slow-growing, locally invasive malignant epidermal skin tumor, and the most common growth patterns are superficial (sBCC) and nodular (nBCC). A variety of surgical and nonsurgical interventions are available to treat sBCC.²⁹ However, the immune system plays a crucial role in the development and pathogenesis of skin cancer, and IM increases the host's immune response against BCC cells. IM offers a minimally invasive therapy, better cosmetic results, and self-application by the patient improves convenience and appeal. Thus, IM is a reasonable treatment option for patients who are not good candidates for surgery, refuse surgery and/or require less aggressive interventions, and can be useful to prevent or defer surgery.

Imiquimod is approved by the FDA for the treatment of biopsy-confirmed, primary nonfacial sBCC in immunocompetent adults, when surgical methods are less appropriate (Figure 64-2). Dose-response studies indicated that the



FIGURE 60-2 Superficial basal cell carcinoma (sBCC) on the trunk prior to treatment.



FIGURE 60-3 Marked erosion and crusting at the end of the treatment with topical imiquimod.



FIGURE 60-4 Clinical resolution of the sBCC after 5 years of follow-up.

highest response rates were associated with more frequent or prolonged dosing, together with a significant inflammatory reaction (Figure 60-3).^{30,31} The optimal application schedule is 5 times per week for a full 6 weeks, and occlusion of the treatment site does not appear to be beneficial.³² Most sBCC achieve complete remission or decrease in size with IM, and short-term studies showed a histopathologic

clearance rate of 82% for IM in the treatment of sBCC.³³ A 5-year follow-up study to evaluate the recurrence rate of sBCC treated with IM revealed 81% sustained clinical clearance rate in those patients who achieved initial clearance (Figure 60-4).³⁴ Finally, open-labeled studies and case reports suggest that IM is an effective alternative for the treatment of sBCC in patients with basal cell nevus syndrome, xeroderma pigmentosum, and immunosuppressed patients.³⁵

Nodular Basal Cell Carcinoma

Nodular BCC (nBCC) is the most common type of BCC. It is a round, shiny, translucent nodule with overlying small blood vessels and a pearly-appearing rolled border. Surgery is the gold-standard treatment, but IM has also been evaluated for nBCC. Short-term studies with patients receiving a once-daily IM dose showed a histopathologic clearance rate of 71% and 76% after 6 and 12 weeks of treatment respectively.³⁶ The clearance rate depended on both the dosing regimen and the size of the tumor, and increasing severity of local inflammatory reactions was associated with higher clearance rates. IM thrice weekly for 8 and 12 weeks in the treatment of nBCC achieved 64% complete histopathologic clearance, with higher efficacy for tumors that were less than 1 cm in diameter.³⁷ In this study, 17% of patients with clinical clearance had pathologic evidence of residual disease. Thus, some authors recommend a test-of-cure biopsy of the nBCC clinically cleared with IM. In addition, anecdotal case reports suggest the efficacy of IM for nBCC in patients with basal cell nevus syndrome and xeroderma pigmentosum.

The combination of curettage of nBCC prior to the use of topical IM was investigated in two studies. In the first, IM was applied daily for 6–10 weeks after curettage, and this produced histologic clearance of 94% cases.³⁸ In the second study, curettage and electrodesiccation followed by IM once daily for 1 month after reduced the frequency of residual tumor and improved the cosmetic appearance.³⁹ Few recurrences have been reported during the short-term follow-up studies, although the results of the 5-year follow-up trials have not yet been published.

Actinic Keratoses

Actinic keratoses (AK) are the most common ultraviolet light-induced lesions and frequently occur on sun-exposed skin. AK is considered as *in situ* squamous cell carcinoma (SCC) that may progress to invasive SCC (iSCC). Although the exact rate of transformation of AK to iSCC is unknown, the majority of iSCC appear to arise from within AK. The treatment of AK provides an important opportunity to prevent the development of iSCC. Cryotherapy is the standard of care for AK, but it does not treat initially inapparent or subclinical AK and recurrences are frequent. IM is an effective and well-tolerated treatment for AK, and it is

approved by the FDA for the treatment of clinically typical, nonhyperkeratotic, nonhypertrophic AK on the face or scalp in immunocompetent adults. IM has to be applied once-daily, twice weekly (USA) or thrice weekly (Australia) for 16 weeks. Another option is the cycle dosing regimen approved in Europe and Australia, that consists of thrice weekly IM application for 4 weeks followed by a rest period of 4 weeks. The cycle dosing regimen may be repeated if any AK remains after completing an 8-week cycle, and the overall complete clearance rate is comparable to the 16-week treatment regimen, while decreasing drug exposure to the patient and decreasing the overall treatment time.⁴⁰

A recent trial demonstrated that IM applied once weekly for 24 weeks was convenient for patients and resulted in improvement of AK with minimal side effects.⁴¹

Subclinical AK lesions may become apparent in the treatment area during treatment with IM. Thus, the fact that IM effectively uncovers and treats subclinical lesions is considered an additional benefit of treatment with the drug. Although treatment rest periods are recommended if marked inflammation occurs, greater severity of erythema, erosions, and crusting appear to be associated with higher clearance rates. Fifty per cent of patients achieve complete clinicopathologic clearance of all AK lesions and an excellent cosmetic result.⁴² A randomized study compared IM, topical 5-FU and cryosurgery for AK, and the clearance rates for the treatment field at 12 months post-treatment were 73%, 33%, and 4%, respectively.⁴³ Thus, IM should be considered as a first line therapy for sustained treatment of AK. Furthermore, long-term follow-up data showed a low incidence of new AK lesions following treatment with IM. After a median follow-up period of 16 months IM continued to provide a long-term clinical benefit in a majority of patients.⁴⁴ IM can also be combined with other therapies for AK, and two RCT demonstrated higher AK clearance rates when IM was applied after cryotherapy or photodynamic therapy.^{45,46}

Immunosuppressed patients are a growing population at increased risk for developing AK and iSCC, thus resulting in significant morbidity and mortality. Two RCTs concluded that IM appears to be an effective alternative for the treatment of AK and cutaneous dysplasia in solid organ transplant recipients.^{47,48}

Other Squamous Intraepithelial Neoplasia

Bowen's disease is an *in situ* SCC of the epidermis and has a 3%-5% risk of developing into iSCC. A RCT revealed that 73% patients treated daily with IM for 16 weeks achieved complete resolution, with no relapse during the 9-month follow-up period.⁴⁹ However, more studies to define the ideal dosing regimen are required before it can be accepted as an approved therapy.

Anogenital intraepithelial neoplasia (AGIN) are generally HPV-associated tumors that may progress to iSCC. Surgery is the cornerstone treatment of AGIN, but

alternatives to surgery are needed because of considerable treatment-associated morbidity and high recurrence rates. Case series suggest that IM is highly effective, more convenient and minimally invasive for AGIN. A prospective follow-up study demonstrated that IM led to a decrease of human papillomavirus DNA and to a sustained clearance of anal intraepithelial neoplasia in HIV-infected men.⁵⁰ A RCT concluded that IM is effective in the treatment of high-grade (2 or 3) vulvar intraepithelial neoplasia.⁵¹ IM was well tolerated, relieved itching and pain, and did not influence health-related quality of life.

Other Cutaneous Malignancies

Open-labeled trials and case series suggest the usefulness of IM for actinic cheilitis, extramammary Paget's disease, lentigo maligna, melanoma metastasis, T cell cutaneous lymphoma and Kaposi sarcoma.

Actinic cheilitis (AC) occurs on the vermillion border of the lips, usually in a patient with significant sun exposure. AC requires early therapy to prevent its progression into iSCC. Topical therapy with IM may be an efficient, cosmetically more appealing alternative treatment than currently used destructive therapies.

Extramammary Paget disease (EMPD) is a rare skin neoplasm found in the genital, anorectal, or axillary area, which can be limited to the epidermis and can sometimes be associated with underlying carcinomas. Surgery is the gold-standard treatment, but case reports suggest that IM is an alternative to surgery.

Lentigo maligna (LM) is a melanoma *in situ* that most commonly appears on the sun-exposed skin of the head of elderly patients. Although LM has the potential for invasion, it often has a greatly protracted radial growth phase and may remain indolent for years. The current standard of care is surgical excision, but complete removal of LM may be difficult because of its occasional extensive subclinical extension. Complete regression of LM after IM treatment has been reported in open-labeled case series. However, without controlled evidence and prolonged follow up, the use of IM for LM must still be considered experimental.⁵² There are also case reports of the successful use of IM for dermal melanoma metastasis, but IM failed to prevent the progression of subcutaneous metastases.

Mycosis fungoides (MF) is the most common clinicopathologic subtype of primary cutaneous T-cell lymphoma. Treatment of MF with IM is well tolerated and associated with a histopathologic and clinical response rate of 50% in open-labeled studies.⁵³ Lymphomatoid papulosis, cutaneous CD30+ anaplastic large cell lymphoma, cutaneous follicle center lymphoma and cutaneous B-cell lymphoma have also been successfully treated with IM. As the long-term recurrence rates after treatment are unknown, patients should have long-term follow-up.

Kaposi sarcoma (KS) is a low-grade vascular neoplasm associated with human herpes virus type 8 infection. An

open-labeled trial demonstrated that IM had antitumor activity in about half the patients with classic and endemic KS and was generally well tolerated.⁵⁴ There are anecdotal reports of the efficacy of IM for immunosuppression-associated KS.

Finally, there are reports of the successful use of IM for keratoacanthoma and iSCC.

Vascular Tumors

Hemangioma of infancy is a benign vascular tumor characterized by presentation within the first weeks of life, rapid growth during the first year and variable degree of spontaneous involution over a period of several years. Active nonintervention remains the mainstay of therapy for most uncomplicated tumors, and the immune system is thought to play a role in the regression phase of hemangioma. Open-labeled studies suggest that IM may be a successful treatment option for superficial hemangioma and recurrent pyogenic granuloma.⁵⁵

Keloids

No effective treatment exists for permanent keloid removal. Case series suggest IM usefulness to prevent the recurrence of excised keloids. However, a recent RCT with 20 keloids failed to demonstrate a significant difference in keloid recurrence rates between the two treated groups. At 6 months, keloid recurrence rates were 37.5% in the IM group and 75% in the vehicle group ($p = 0.54$).⁵⁶

Other Skin Disorders

There are open-labeled case series and individual case reports of the successful use of topical IM for infiltrative BCC, trichoepitheliomas, epidermolytic acanthomas, porokeratosis of Mibelli, elastosis perforans serpiginosa, angiolympoid hyperplasia with eosinophilia, vulvitis circumscripta plasmacellularis, Zoon's balanitis, discoid lupus erythematosus, localized scleroderma, granuloma annulare, granuloma faciale, silicone granuloma, chronic interdigital tinea pedis and alopecia universalis. However, the role of IM in the treatment of these conditions remains unclear, and RCT are warranted.

SAFETY PROFILE

Studies on acute dermal toxicity, dermal irritation, dermal sensitization, and repeat-dose dermal toxicity have demonstrated that IM 5% cream is slightly irritating. IM does not enhance ultraviolet radiation-induced damage to human epidermal cells or DNA and has no detectable potential for inducing either photocontact allergy or phototoxicity in humans.⁵⁷ According to the results of five in vitro and three in vivo genotoxicity tests, IM showed no mutagenic or clastogenic potential. No appropriate or well-controlled studies

have been conducted in pregnant women, so safety of IM use during pregnancy remains uncertain and IM carries an FDA pregnancy C classification. IM should only be used in pregnancy if potential benefits surpass potential risks to the fetus. Furthermore, it is not known whether topical IM is excreted in breast milk.¹⁴

The most frequently reported adverse reactions are skin and application site reactions, although some patients develop systemic reactions. Typically, these reactions are more frequent and intense as dosing frequency increases, and decrease in intensity or resolve after cessation of IM therapy. Local skin reactions are frequent, generally mild, and well tolerated, and may extend beyond the application site onto the surrounding skin. However, treatment should be discontinued for some time in some patients because of the intensity of local reactions. Proper counseling on the related side effects is critical for maintaining patient compliance.

These skin reactions include: erythema, edema, induration, vesicles, pustules, erosion, excoriation, ulceration, weeping, exudate, flaking, scaling, dryness, scabbing, crusting, itching, soreness, and burning. Despite skin reactions, patients generally experience excellent cosmetic outcome. However, localized postinflammatory hyperpigmentation, hypopigmentation, and vitiligo may follow IM therapy, and these changes may be permanent.

The systemic reactions are uncommon and disappear rapidly on discontinuation of the drug. Systemic reactions that may be related to IM 5% cream are fatigue, fever, malaise, pain, myalgia, arthralgia, headache, nausea, diarrhea, and influenza-like symptoms. Rarely, IM may trigger or exacerbate inflammatory conditions such as psoriasis, aphthous ulcers, pemphigus, myasthenia gravis, and angioedema. Thus, IM should be used with caution in patients with pre-existing autoimmune conditions.

The effect of treatment with IM on the health-related quality of life (HRQL) of patients has been rarely studied. A RCT comparing IM and placebo in 52 women with vulvar intraepithelial neoplasia concluded that IM does not influence HRQL. In a repeated-measures analysis, no significant differences at baseline, at 4 weeks after treatment, or at 12 months were observed in self-reported HRQL, body image, or sexuality.⁵¹

CONCLUSION

A variety of factors affect the best treatment for a particular patient. The main aims of treatment are to cure the patient, to preserve function, to achieve an optimal cosmetic result, and to consider the needs and desires of the patient. The choice of therapy depends on clinical circumstance and medical practitioner experience. Moreover, patients should be educated about the available surgical and nonsurgical treatment options for their skin disease. The risks/benefits, postoperative requirements, potential complications, and long-term outcome should be discussed. The possible need

What We Know

- IM is a small synthetic imidazoquinoline heterocyclic amine of 240.3 Da (C14H16N4).
- IM is an immune response modifier that acts through toll-like receptor 7 to induce cytokine production and subsequent innate and adaptive cell-mediated immune response.
- IM induces frequent local skin inflammatory reactions, generally mild and well tolerated. Systemic reactions are uncommon and disappear rapidly on discontinuation of the drug.
- Meta-analysis of RCT has demonstrated the efficacy of IM for AGW, sBCC and AK, and these indications are approved in USA, Europe, and Australia.
- There is good evidence to support the use of IM in the treatment of AGW in HIV-positive patients, cutaneous leishmaniasis in combination with parenteral pentavalent antimony, nodular BCC, AK, and skin dysplasia in transplant recipients, Bowen's disease, high grade VIN and prevention of recurrence of shaved keloids, but these indications are currently off-label.
- Open-labeled trials and case reports suggest IM efficacy for many other skin conditions, but RCT are warranted.

for further treatment or long-term follow-up should also be outlined. Lastly, all patients must be made aware of the likely cosmetic/functional outcome, as well as the costs of the proposed treatment. Taking the above-mentioned into account, IM offers a topical, noninvasive, nonsurgical, home-based therapeutic option that has revolutionized the therapeutic management of cutaneous infections and skin cancer, empowering patients to participate in their own treatment.

IM is an immune response modifier drug, that applied topically induces production of several cytokines and chemokines, which promote both innate and adaptive cell-mediated immune responses. IM has frequent local side effects and uncommon systemic reactions that disappear rapidly on discontinuation of the drug. Patient selection and counseling are critical for optimizing compliance with respect to managing expectations and anticipated application-site reactions.

Imiquimod is currently approved by the FDA for the treatment of AGW, sBCC, and AK. Moreover, the use of IM has gradually expanded to various off-label skin conditions in the last decade. RCT have demonstrated IM efficacy for AGW in HIV-positive patients, cutaneous leishmaniasis in combination with parenteral pentavalent antimony, nodular BCC, AK, and skin dysplasia in transplant recipients, Bowen's disease, high grade VIN, and prevention of recurrence of shaved keloids. Based on the currently available data, topical IM appears to have a role

in treating these skin diseases if the benefit-to-risk ratio is favorable, although there are currently limited long-term follow-up data.

Open-labeled studies and anecdotal case reports suggest IM is a safe and effective across a broad range of cutaneous diseases. However, the role of IM in the treatment of these conditions remains unclear, and in the absence of RCT clinicians must consider the cumulative weight of smaller studies with their personal experience when assessing appropriateness of off-label IM use.

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Topical Tar

61

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SUMMARY

Coal tar and wood tar have been utilized in the field of modern dermatology for many years, dating back to ancient times. Tar is used to treat many dermatologic conditions, including chronic stable plaque psoriasis, scalp psoriasis, atopic dermatitis, and seborrheic dermatitis, either alone, or in combination therapy with other medications and/or phototherapy. Tar has been shown to be very effective in the clearing of lesions and prolonged remission times. However, many patients do complain of its odor, messy application and staining of clothing, but modified tar preparations have been made to increase their acceptability. Recent clinical studies do not support the possible carcinogenicity of tar. This article will review the current uses of tar in the treatment of selected dermatologic conditions as well as the pharmacology, formulations, efficacy, and adverse effects.

INTRODUCTION

Tar has been used in medicine since the ancient times, as described by Hippocrates.¹ Over 2000 years ago, Dioscorides, a Greek physician and pharmacologist, was one of the first physicians to use coal tar for dermatologic conditions. In 1681, therapeutic crude coal tar in dermatology was emphasized by Becher and Serle.^{2,3} In 1895, Professor Kaposi⁴ noted tar as being an important part of his pharmacopoeia. Through dry distillation, tar was obtained from coals, stones, and several kinds of wood including birch, beech, and *Juniperus oxycedrus*.

In the past, coal tar has been used to treat many different types of dermatologic conditions including scabies, sarcoidosis, pityriasis lichenoides chronica, and neurodermatitis. Coal tar is currently employed to treat chronic stable plaque psoriasis, scalp psoriasis, atopic dermatitis, seborrheic dermatitis, and occasionally neurodermatitis.^{3,5-7} Goeckerman was the first to describe the clinical efficacy of ultraviolet (UV) radiation in combination with coal tar for the treatment of psoriasis, allowing for long remission times and high clearing rates.⁸ Coal tar is considered the first line treatment in many parts of the world despite its lack of use in the western world.^{6,9} As evidenced by clinical experience and patient trials, tar is effective in treating many skin disorders. Currently, there are a few controlled

clinical trials. This is likely because of many factors, including a lack of interest by manufacturers, the introduction of newer and more lucrative therapeutic modalities, and the concerns regarding carcinogenicity. When treating patients, other tars, including wood tars, are also occasionally used instead of coal tar, but may not be as effective.¹⁰

PHARMACOLOGY OF TAR

Crude coal tar, wood tar (principally pine, beech, birch, and juniper) and shale (bituminous tars/ichthammols) are the three main types of tar.¹⁰ Wood and shale tars lack photosensitizing effects and contact sensitizing potential, unlike that of coal tar. Coal tar is heavier than and slightly soluble in water, resulting in a mildly alkaline solution with a naphthalene-like odor and a sharp, burning taste.¹¹ In the absence of air, coal tar is formed by heating coal. The gases that form are then allowed to cool into a brown-black liquid.² Ammonia is then removed, resulting in a product containing 10,000 compounds, including polycyclic aromatic hydrocarbons (PAHs), water, and carbon. This crude coal tar then undergoes fractional distillation. The oils that are then produced can be mixed in various topical vehicles, allowing for increased absorption of the coal tar.^{2,3} Depending on the type of coal used and temperature of the distillation, the final composition can vary greatly.¹² For example, coal tar has an increased content of phenols and tar acids at lower temperatures. In comparison, coal tar has an increased number of PAHs at higher temperatures.² At this time, there are no agreed upon chemical or biologic standards to determine the exact pharmacokinetics of coal tar given the variability expected in the final formulation.¹

Mechanism of Action

The mechanism of action of topical tar is not well understood. There are, however, several possible effects. These include suppression of DNA synthesis, which leads to a reduction of epidermal hyperproliferation in psoriatic skin¹² (Table 61-1). On the other hand, coal tar increases the mitotic rate-labeling index, causing an initial thickening of the epidermis in healthy skin.¹⁰ The variance in activity is likely attributed to coal tar correcting a defect in differentiation in psoriatic skin. Furthermore, antibacterial,

TABLE 61-1—Possible Mechanisms of Action of Coal Tar^{2,3,12}

Suppression of DNA synthesis
Reduction of epidermal hyperproliferation
Antifungal
Antibacterial
Antiparasitic
Antipruritic
Vasoconstrictive
Keratoplasic and antiacanthotic
Atrophogenic effect on epidermis
Photosensitizing effect
Inhibition of sebum secretion
Anti-inflammatory

antifungal, antiparasitic, antipruritic and anti-inflammatory effects have been documented with the use of coal tar.^{2,3} In addition, inhibition of sebum secretion was reported with the use of topical therapy in animal studies.²

Within the range of 330-550 nm in the UVA and visible light spectrum, coal tar possesses a photosensitizing effect, but the relevance of this is not fully understood and may be attributed to the tar components, specifically anthracene, 3,4 - benzpyrene, fluoranthene and pyrene.^{2,3,12} In mouse models, the use of coal tar with near UVA light has been shown to lead to suppression of DNA synthesis in normal and proliferating skin when compared to coal tar use alone.¹³ This has not been noted with UVB or UVC treatment.¹⁴ Given the phototoxic smarting reactions that UVA light causes, as well as the relatively necessary long exposure times, UVA light is not used.¹ Compared to tar and UVA light, tar and UVB light demonstrate increase efficacy in psoriasis therapy.¹⁰ The use of low-dose narrow-band UVB with a topical coal tar preparation (liquor carbonis detergens) has been shown to be an effective combination,¹⁵ but has not been proven to be preferable to broadband UVB with a topical coal tar preparation.

Formulations and Pharmacokinetics

Given its color, odor and ability to stain clothing, the use of tar has decreased in part because of concerns that the application is physically unappealing.¹⁶ A recent study compared both the tolerability and cosmetic acceptability of liquor carbonis distillate (coal tar) 15% solution versus calcipotriene cream in the treatment of plaque psoriasis. Patients were asked to rate the scent, drying time, staining, and dab-on applicator for the coal tar solution. Overall, patients reported the 15% coal tar solution as a cosmetically acceptable and tolerable treatment when compared to calcipotriene cream.¹⁷ Currently, crude coal tar (pix carbonis), coal tar ointment, and coal tar solution are the

only official USP preparations¹¹. Extracts of tar or alcoholic solutions have been used as plain solutions and/or incorporated into ointments. Topical tar solutions (liquor picis carbonis or liquor carbonis detergens- LCD) are prepared by mixing 50 g of polysorbate 80, 200 g of coal tar, and a quantity of alcohol sufficient to make 1 L. The final products usually contain different tar fractions; therefore, variance in the effectiveness of these formulations can be expected.^{1,18} Coal tar extracts are made using different solvents, which can include polyoxyethylene lauryl ether. Coal tar (1- 20%) extracts have been dissolved in gels, lotions, and shampoos in order to increase their cosmetic acceptability.² Because exposure to air increases the viscosity of these products, they should be stored in tight containers¹⁸ (Table 61-2).

Keratolytic agents, such as 5% salicylic acid, can be incorporated into these preparations to aid in the reduction of scaling.¹⁶ For difficult-to-treat palmar and plantar psoriasis, the use of tar with a corticosteroid cream is especially useful under occlusion.¹⁴ Many of these products can be found in pharmacies specializing in compounding. However, obtaining the compounded products can be extremely difficult.⁶ Currently, there are some commercially available compounded products (Table 61-3).

Efficacy is determined by both the strength of the tar as well as the vehicle in which it is dissolved. In one large study, investigators compared 1% coal tar lotion prepared with a liposomal base to 5% conventional coal tar extract in the treatment of patients with mild to moderate chronic plaque psoriasis. The total sign score (an assessment rating for erythema, induration and scaling) for 2 target plaques

TABLE 61-2—Tar Preparations¹⁰

Crude coal tar
1% Crude coal tar in petrolatum, starch, and zinc oxide
2% Crude coal tar in petrolatum (with and without 5% salicylic acid)
3% Crude coal tar in petrolatum, starch, and zinc oxide
5% Crude coal tar in petrolatum, starch, and zinc oxide
LCD preparations
10% LCD in hydrophilic ointment (with and without 5% salicylic acid)
10% LCD in petrolatum (with and without 5% salicylic acid)
10% LCD in petrolatum (with and without 5% salicylic acid)
15% LCD with betamethasone 0.025% in hydrophilic ointment
Scalp tar preparation
10% LCD in Nivea oil*
20% LCD in Nivea oil*
Tar pomade (mixture of LCD, Tween 20, salicylic acid, and hydrophilic ointment)

LCD, Liquor carbonis detergens = coal tar solution.

(Formulations adapted from Baylor Psoriasis Center, Dallas, TX, and New York Skin and Cancer Unit, New York, New York.)

*Manufactured by Beiersdorf, Hamburg, Germany.

TABLE 61-3—Selected Tar Products¹⁷

Products	Active ingredients	Dosage forms	Manufacturers
Coal tar solutions (LCD)			
Cutar	7.5% LCD (1.5% coal tar)	Lotion or mixed with water as soak	Summers Laboratories, Collegeville, PA
Psorigel	7.5% LCD (1.5% coal tar)	Gel	Healthpoint, Fort Worth, TX
Ionil-T	5% LCD (2% coal tar)	Shampoo	Healthpoint, Fort Worth, TX
Tarsum	10% LCD (2% coal tar) and 2% salicylic acid	Shampoo	Summers Laboratories, Collegeville, PA
Crude coal tar (pix carbonis)			
Estar	5% Coal tar	Gel	Bristol Myers Squibb, New York, NY
Coal tar extract			
T/Gel	2% (0.5% Coal tar)	Shampoo	Neutrogena, Los Angeles, CA
	4% (1% Coal tar)		
Coal tar distillate			
Doak tar	3% (1.2% Coal tar)	Shampoo	Doak, Nycomed USA, Melville, NY
Doak tar oil	2% (0.8% Coal tar)	Solution, mixed with water for soak	Doak, Nycomed USA, Melville, NY
Doak tar distillate	40%	Solution for compounding	Doak, Nycomed USA, Melville, NY
Tar blends			
Polytar	2.5% (0.5% Coal tar)	Soap (with povidone)	Steifel, Coral Gables, FL
	4.5% (0.5% Coal tar)	Shampoo	
	Both products contain a solution of crude coal tar, coal tar solution, juniper tar (cade oil), and pine tar		

LCD, liquor carbonis detergens = coal tar solution.

was significantly decreased in the 1% group. In addition, cosmetic acceptability of both products was not significantly different. The greater efficacy found in the lower strength product was attributed to the vehicle disrupting the architecture of the intracellular lipids, which allows for increased transport of the active ingredient into the epidermis.¹⁹

Furthermore, length of application has to be considered. In a paired comparison evaluating the use of short-term crude coal tar therapy in patients with chronic stable plaque psoriasis, 17 patients applied 30% crude coal tar treatment for 1 hour to one affected area and 5% crude coal tar treatment for 23 hours daily to another affected area for 21 days. Compared to plaques coated with the higher strength tar, the plaques covered with 5% crude coal tar showed significant improvement at days 14 and 21, as measured by severity scores assessing for erythema, scaling, and thickness.²⁰

Application of Tar

In 1895, Kaposi⁴ wrote, "The tar is usually applied in the following manner: the psoriatic patches having been cleared of their epidermis by soap in the bath, a thin layer of tar is rubbed in energetically once or twice a day, or at night

only, by means of a bristle brush, after which the patient dresses in flannel clothes. This procedure is repeated every day." In order to achieve a better effect, Kaposi described a tar bath in which the patient is first rubbed thoroughly with soap, then immediately has all affected skin painted with tar, which was left in place for 4-6 hours. However, he did note that acute tar toxicity was a potentially serious side effect.

Currently, tar can be used up to four times a day for skin disorders. Making sure that it is not applied to any bleeding or raw plaques, it is massaged into the skin and left on for at least 2 hours. Avoiding plastic wraps to prevent irritation, it can be wrapped in bandages. An emollient can be used 1 hour after the tar preparation is applied if the skin is excessively dry after treatment. For bath soaks, the tar is mixed with water. For about 30-45 days, the patient is to soak him or herself for approximately 15 minutes, once daily or even twice weekly. Tar should be removed from the body prior to ultraviolet radiation when administering phototherapy, which can be given 2 to 72 hours after the tar application.¹⁸ Tar shampoo, when used for the scalp, is used twice a week. It is applied to the scalp while hair is wet. Patients are instructed to stroke the hair in the direction of hair growth, followed by a rinse.

Pregnancy, Lactation, Child Use

Physicians should use caution when prescribing tar to a gravid patient, as the use of tar in pregnancy has not been studied. Overall, tar products are not generally prescribed in pregnant patients.⁶ Nursing mothers should also be informed about the lack of data regarding excretion of tar into the breast milk. In addition, the safety profile of tar in children has not been established. Clinical judgment should be used regarding tar use in children.¹⁸

Indications

Coal tar is used primarily in patients with chronic stable plaque psoriasis, scalp psoriasis, seborrheic dermatitis, atopic dermatitis, and occasionally neurodermatitis. If the psoriatic patient is sun sensitive or taking photosensitizing medications, if folliculitis or acne is evident in the area to be treated and in acute inflammatory psoriasis, tar should be avoided, as it may precipitate an erythroderma.^{18,21}

Chronic Stable Plaque Psoriasis

The original Goeckerman regimen had patients soak in crude coal tar for the majority of the day and night. After removal of the tar, this was followed by gradually increased exposure to UV radiation via a quartz mercury vapor lamp.²² This regimen required occlusive dressings and hospitalizations for 2 to 3 weeks, but did lead to a high clearing rate and long remissions.⁸ Because it is cheap, effective, and available, the original Goeckerman regimen is still used in most of the world for the treatment of chronic plaques psoriasis.²³ To make it more practical for outpatient treatment, many modifications have been made. Conflicting data has accumulated regarding the efficacy of this treatment, with several studies comparing tar to petrolatum in ultraviolet therapy showing no enhanced therapeutic benefit of the tar with erythemogenic doses of UV radiation.²⁴⁻²⁹

One modified Goeckerman regimen consists of the patient applying tar ointment at bedtime. After removing tar from body surfaces in the morning, the patient undergoes UV exposure. Good to excellent results in 95% of patients was shown in a study comprised of 123 psoriasis undergoing this regimen with daily UV irradiation and thrice-daily tar ointment application for an average of 20 days. These patients also demonstrated remission rates averaging 1.7 years with a range of 2 months to 8 years.³⁰ In addition, the remissions on tar therapy were longer than the spontaneous remissions experienced during the natural course of their disease. In a 21-day evaluation of the use of this modified ambulatory Goeckerman regimen on 162 severe psoriatic patients, all patients were hospitalized for 14 days. On day 14, about half of these patients were discharged to an outpatient setting. With 60% of patients still in remission 2 years after treatment, there was no

significant difference regarding the improvement of psoriasis in either group after discharge.³¹ Furthermore, studies have also shown that applying tar 2 hours prior to irradiation is equally effective as using overnight.³²

Several studies have compared the use of topical tar with other standard topical treatments of stable plaque type psoriasis. In one study of 40 patients, 1% coal tar preparation (Exorex)TM was compared with calcipotriol cream in patients with plaque-type psoriasis. Both topical medications were found to be comparably effective; however, cosmetic acceptability and tolerability was better for calcipotriol.³³ Furthermore, a study comparing topical 0.1% tazarotene gel with crude coal tar 5% ointment in patients with stable plaque psoriasis demonstrated comparable clinical efficacy.³⁴

Scalp Psoriasis

Scalp psoriasis affects 50% of psoriatic patients.³⁵ Particularly if pruritus is a main complaint, coal tar is effective in the treatment of scalp psoriasis. These coal tar preparations are usually mixed into a lotion or gel formulation. These can also be combined with a corticosteroid if needed.³⁶ Tar preparations are still an effective and cheaper alternative that extends the remission time if used as maintenance therapy in comparison to other treatments, including corticosteroids and calcipotriol in the treatment of scalp psoriasis³⁵. In addition, some tar preparations, such as gels, may not need occlusion, while shampoos may not be as effective without occlusion.³⁵ Adding salicylic acid can be helpful in removing thick scales, thus allowing for better topical absorption of tar.

In one large study, a gel containing coal tar was used in psoriatic patients for 5 consecutive days, followed by a vegetable oil soak on the 6th day. Eighty-three percent of patients cleared or showed marked scalp improvement. In addition, only 37.6% of them needed 2–4 courses. To assess for duration of remission, 72 patients that responded went on to either use a tar or non-tar shampoo twice a week. The use of a tar-containing shampoo allowed for a median remission time of 8 months, in comparison to those who used the non-tar shampoo relapsed in under half that time.³⁵

Seborrheic and Atopic Dermatitis

Few controlled clinical studies have been done to support the use of tar in the treatment of seborrheic and atopic dermatitis. However, tar has been used to treat these conditions for many years. Its use for these diseases dates back to ancient times and is cited in many texts.^{1,2,37-40}

To avoid possible side effects, including percutaneous absorption, local effects such as thinning of the skin, and in rare cases, adrenocortical function suppression, coal tar preparations in seborrheic dermatitis avoids the use of

corticosteroids.^{5,37} According to one pharmacologic study, coal tar gel use against *Malassezia* species, fungi isolated from seborrheic dermatitis patients, resulted in antifungal activity in vitro based on minimum inhibitory concentration measurements.⁴¹ The in vitro fungistatic effects against *Malassezia* species seen in coal tar have been found to be equivalent to ketoconazole gel.⁴²

The use of coal tar preparations has been shown to be beneficial in the treatment of atopic dermatitis. Crude coal mixed with a zinc paste base was applied 2 to 3 times a week in an outpatient analysis involving 18 atopic patients. They were then compared to others in an inpatient setting treated for the same condition with daily applications of the same treatment. Comparable improvements were shown in both groups, as measured by a visual scoring system.⁷

ADVERSE EFFECTS

Because of a chlorine-containing ingredient, tar is a follicular irritant, and tar folliculitis a common side effect of coal tar. This is usually evident on the lower extremities with tar concentrations greater than 2%.² Acneiform eruptions have also been noted with the use of tar; however, this differs from acne vulgaris because the main inducer in this case is chlornaphthalene. This is mainly seen in patches on the extensor surfaces of the arms, with pruritus as the main complaint. In addition, there is an association with dermatitis venenata of the fingers.³⁷ Adverse effects of tar can also include exacerbation of psoriasis and application site reactions, such as irritation, rash, burning, and stinging.¹⁹ Furthermore, allergic contact dermatitis, telangiectasias, atrophy, pigmentation, keratoacanthomas, and exfoliative dermatitis can also occur.^{2,3} These adverse effects are treated in the standard way. However, approaches beneficial for acne, folliculitis, and contact dermatitis are unlikely to be effective until the topical tar has been terminated or suitably modified. Kaposi⁴ described long ago tar intoxication, symptomatic of acute tar absorption. This includes symptoms such as nausea, vomiting, and black urine (Table 61-4). Unless it is actually ingested or absorbed in large amounts, the risk of tar intoxication is small. One should avoid using tar in erythrodermic psoriatic patients or extensively in a young child.

Carcinogenicity

Since 1775 when Sir Percival Pott linked chimney sweepers with an increased risk of scrotal cancer, there have been concerns raised about the carcinogenicity of coal tar. Small nodules that develop from cutaneous exposure to tar are known as tar keratoses. They may spontaneously regress or fall off, but have the potential to develop into a squamous cell carcinoma. In one study, 46 of 111 patients who were exposed to tar occupationally for 40 years, developed a cutaneous carcinoma.¹⁴ Topical tar treatment have resulted in percutaneous absorption, as measured by blood and

TABLE 61-4—Possible Side Effects of Coal Tar^{2,3,18}

Local irritation
Tar folliculitis
Acneiform eruptions
Application site reactions
Exacerbation of psoriasis
Dermatitis medicamentosa
Burning and stinging
Allergic contact dermatitis
Atrophy
Telangiectases
Pigmentation
Exfoliative dermatitis (erythroderma)
Keratoacanthomas
Acute tar toxicity: tarry black urine, nausea, vomiting

urine samplings in animal models.² Polycyclic aromatic hydrocarbons (PAHs), especially benzo(a)pyrene, are converted into the active form by inducible microsomal enzymes, which then bind to nucleotides of RNA and DNA, causing carcinogenic effects as seen in animal studies^{14,43} (Figure 61-1). However, there is no conclusive epidemiologic evidence supporting the human use of topical tar preparations leading to skin cancer.⁴⁴

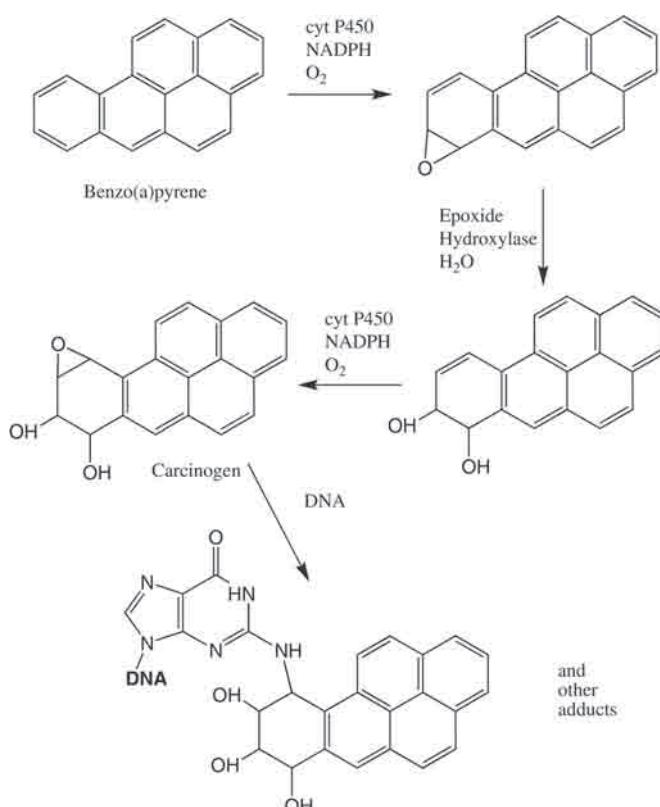


FIGURE 61-1 Mechanism of metabolic activation of benzo(a)pyrene leading to alkylation of DNA.

In a relatively small study of 23 patients, each underwent the Goeckerman regimen for an average of 17 days with an endpoint of determining the genotoxic effects.²³ Measurement of certain selected biomarkers including metabolites of PAHs, urinary thioethers, and chromosomal aberrations of peripheral lymphocytes were obtained. The results demonstrated that patients could be endangered at peak genotoxic exposure; however, these markers were not long lasting. These markers were not present after the 78th day of therapy. PAHs are primarily responsible for the genotoxicity in tar; however, UV light may as well be a contributing factor. Six males were treated for psoriasis with either topical pure coal tar or 4% coal tar-containing ointment in order to assess their genotoxic risk.⁴⁵ The frequencies of chromosome aberrations and sister chromatid exchanges in lymphocytes as well as urinary mutagenicity levels were related to the levels of exposure to coal tar. This lymphocytic circulation implies extracutaneous systemic carcinogenic risk. Furthermore, a recent study involving 13,200 patients with psoriasis and eczema showed no increased risk of non-skin or skin malignancies after coal tar treatment with a median treatment duration of 6 months.⁴⁶ However, more well-designed epidemiologic surveys should be performed to assess the risk of cutaneous and bladder cancer, lymphoma, and other malignancies after dermatologic use of coal tar as currently there is still no clear evidence of an increased risk of skin or internal cancers to date.

In a study examining the safety of tar in 719 psoriatics, compared to the general population, there was no increase in the incidence of skin cancer.⁴⁷ In two separate 25-year follow-up trials of 280 psoriatics and 426 atopic and neurodermatitis patients, treated with coal tar and UV radiation, there was no increased risk of skin cancer compared to the general population.^{45,48} The use of UV light appears to potentiate the carcinogenicity of coal tar; however, there has not been a consensus of epidemiologic studies to support this.²³ Overall, the risk of skin cancers in the general population and the prior use of other mutagenic agents needs to be considered when evaluating these concerns.

THE OTHER TARS

Wood tars are derived from the destructive distillation of pine, beech, birch, and juniper. They contain acetic acid or phenolcarbonylic acids, with a relative absence of toxic anthracene and pyridine derivatives.^{1,49} Wood tars have been used in the treatment of many different skin disorders, including psoriasis and atopic dermatitis. Wood tars have no photosensitizing effects.³ Wood tars have been shown to have an increased risk of irritation and allergic sensitization.^{2,10} In one study involving 1,883 patients, 5.4% of patients had wood tar sensitization. In those patients that had a combined allergy to wood and coal tar, cross-sensitization was determined to be the underlying cause.⁵⁰ Furthermore, a patient had exposure to topical pine tar only; however, she also showed a positive reaction to coal

tar, beech tar, birch tar, and juniper tar, supporting the finding that these reactions are a consequence of cross-sensitization and not prior exposure.⁵¹

Wood Tar

Polytar® is a tar blend of coal tar, juniper tar (cade oil), and pine tar and has been employed clinically for the treatment of psoriasis, seborrheic dermatitis, and eczema. In a 6-week, open label, noncomparative trial comprised of 910 patients, topical scalp treatment for seborrheic dermatitis was evaluated in patients using zinc pyrithione 1% mixed in a shampoo base and a tar blend 1% shampoo (Polytar®). Patients were advised to use the shampoo twice weekly for 4 weeks, followed by once a week for 2 additional weeks. Results showed a statistically significant decline in mean dandruff score, with an 84.8% reduction at 6 weeks. Furthermore, mean scores of itching and erythema were statistically decreased.⁵² In another 4-week study with 162 patients in treating moderate to severe scalp psoriasis, tar blend 1% shampoo (Polytar®) was compared to clobetasol propionate 0.05% shampoo (Clobex®). Decreasing erythema, plaque thickening, pruritus, desquamation, and the total and global severity scores were significantly more effective with the corticosteroid shampoo. Patients also preferred the corticosteroid shampoo in regards to cosmetic acceptability in comparison to the tar shampoo.⁵³ Side effects of tar blend shampoos are similar to those of coal tar used alone when topically applied. However, adverse effects such as fever, hypotension, renal failure, and hepatotoxicity have been reported if accidentally ingested.⁵⁴

Shale Tar

Obtained from the destructive distillation of stones that contain fossilized fish, shale tar is composed of 20% sulfur. It has less photosensitizing effects and contact dermatitis potential in comparison to wood or coal tars.³ Shale oil is derived from sedimentary rock. It is further distilled into pale and dark shale oil by different processing methods.⁵⁵ In 1882, the dark shale oil was described in the treatment of skin disorders by Unna; however, it is the pale sulfonated shale oil (PSSO) that is now preferred in the treatment of skin disorders.⁵⁵ Shale tar has been shown to have antibacterial, antimycotic, analgesic, antipruritic, and anti-inflammatory properties. Enhanced proliferation and growth factor expression of keratinocytes, as well as the stimulation of wound healing (epithelialization) have been demonstrated in vivo.⁵⁵ Shale tar is used in the treatment of psoriasis, seborrheic dermatitis, and atopic dermatitis.^{55,56} The anti-inflammatory effect of 0.5% hydrocortisone cream is comparable to 4% shale oil.⁵³

In a randomized, controlled, multicenter, observer-blinded trial comprised of 119 patients evaluating the efficacy of PSSO in the treatment of venous leg ulcers, approximately half of the patients received a topical application of 10%

What We Know

- Tar has been used for centuries and is a proven, effective treatment modality for many skin disorders, including psoriasis, atopic dermatitis, and seborrheic dermatitis. With conflicting evidence in epidemiologic and human studies, there are concerns regarding its carcinogenicity.
- Tar is used in many countries and is considered a first line treatment because of cost savings and availability.
- Tar is a pharmacologic agent that has shown significant efficacy in psoriasis, atopic dermatitis, and seborrheic dermatitis.
- Tar should be considered a key component in the armamentarium of drugs for the treatment of many skin disorders.

PSSO to the site daily for 20 weeks. The other half of patients received a topical vehicle for the same period. As measured by photoplanimetry, the ulcer size was significantly reduced in the PSSO group compared to vehicle, with a cumulative relative reduction in ulcer area greater in the PSSO area as early as 6 weeks into treatment. However, at the end of the study period, there were no significant differences in granulation and complete epithelialization.⁵⁶

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As our understanding of disease mechanisms and clinical experience with these medications continue to grow, so will the prevalence of biologic use. Biologic medications can be loosely defined as bioengineered agents, generally monoclonal antibodies, or soluble cell surface proteins, which are produced in living organisms and interact with cell signaling pathways to improve disease outcomes. Within the scope of dermatology, biologics modulate several fundamental pathways of the adaptive immune system. These powerful agents can dramatically alter the disease activity of psoriasis, autoimmune blistering disease, and a host of other inflammatory conditions. Caution and prudent patient selection must be addressed, however, given the increased risk of infection and malignancy identified in some agents.

TNF-ALPHA BLOCKING AGENTS

Tumor necrosis factor (TNF)-alpha is a potent immunoactivator, which is principally released by cells in the

macrophage/monocyte lineage, along with multiple other cell types, in the early stages of inflammation^{1,2}. The release of TNF-alpha is important in propagating the host response in combating various viral, bacterial, and parasitic infections. Both exogenous (e.g., lipopolysaccharide) and endogenous (e.g., interleukin 1 β and interferon γ) mediators can stimulate TNF-alpha release². Downstream effects are numerous, including endothelial cell activation (allowing for selected and upregulated leukocyte migration and transport), neutrophil activation, macrophage, and NK cell killing, and NF-kappa beta pathway upregulation^{1,2}. Elevated levels of TNF-alpha have been identified in numerous diseases including Crohn's disease, rheumatoid arthritis (RA), psoriasis, psoriatic arthritis, septic shock, and bacterial meningitis²⁻⁵. Inhibition via TNF-alpha blockers is effective in treating psoriasis, Crohn's disease, rheumatoid arthritis, and various other inflammatory diseases (Table 62-1)⁶⁻⁸. There are currently five TNF-alpha blockers on the market in the United States, only three of which are approved for dermatologic use (see Table 62-1).

TABLE 62-1—Tumor Necrosis Factor Inhibitors and Indications(9)

TNF blocker	FDA-approved indications: Dermatology	FDA approved indications: Nondermatology	Off-Label Dermatologic Uses
Infliximab(10)	Severe chronic plaque psoriasis	Crohn's disease Ulcerative colitis Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis	Pyoderma gangrenosum Hidradenitis suppurativa Cutaneous sarcoidosis Behçet's disease Wegener's granulomatosis Pityriasis Rubra Pilaris Dermatomyositis
Etanercept (10)	Moderate to severe chronic plaque psoriasis	Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis Juvenile idiopathic arthritis	Pyoderma gangrenosum Hidradenitis suppurativa
Adalimumab (10-12)	Moderate to severe chronic plaque psoriasis	Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis Juvenile idiopathic arthritis Crohn's disease	Cutaneous sarcoidosis Pyoderma gangrenosum Dissecting cellulitis Granuloma Annulare Behçet's disease
Golimumab	None	Psoriatic arthritis Rheumatoid arthritis Ankylosing spondylitis	No studies as of 5/09
Certolizumab	None	Crohn's disease	

No generics currently exist for any of the TNF-alpha inhibitors. Although the TNF-alpha blockers exhibit class effect, differences exist in efficacy, safety, and mechanism of action.

ETANERCEPT

Etanercept is a dimeric fusion protein which links a portion of the human extracellular TNF-binding receptor to the human Fc portion of IgG1⁶. In addition to TNF alpha, this soluble receptor molecule also neutralizes lymphotoxin A². Etanercept has been approved by the FDA for treatment of psoriasis, psoriatic arthritis, rheumatoid arthritis, ankylosing spondylitis, and juvenile idiopathic arthritis⁶. Off-label uses are numerous. The relevance of added lymphotoxin A blockage is unknown; in one case of rheumatoid arthritis, treatment with etanercept showed improvement, although prior treatment with infliximab (TNF alpha inhibition alone) was ineffective¹³.

Dosing

Etanercept is delivered subcutaneously through syringes or auto-injectable pens. The psoriasis dosing varies per indication and age (Table 62-2).

Efficacy

Psoriasis

A number of trials have proven efficacy for etanercept use in psoriasis. A Phase III randomized double-blind dose reduction study (*n*=583) evaluated the use of etanercept up to 24 weeks in adults with chronic plaque psoriasis,

involving at least 10% body surface area (BSA)¹⁴. Forty nine percent of subjects treated with 50 mg twice a week (BIW), 34% treated with 25 mg BIW, and 3% of placebo patients achieved a psoriasis area and severity index (PASI) score of 75% or greater (PASI 75) at 12 weeks. All subjects from weeks 12 to 24 were transitioned to 25 mg BIW; at 24 weeks 54% of the 50 to 25 mg BIW group, 45% of the continuous 25 mg BIW, and 28% of the placebo to 25 mg BIW group achieved PASI 75. No neutralizing antibodies formed during the study, although antietanercept antibodies developed in about 1% of participants. Although the dose-reduction group (50 mg to 25 mg BIW) showed little change in PASI 75 at 24 weeks, an earlier study showed progressive improvement in treating from 12 to 24 weeks with etanercept at 50 mg BIW¹⁵. For the 50 mg BIW group in the latter study, the PASI 75 at week 12 was 49% and 59% at week 24.

Another Phase III randomized, double-blind trial of etanercept (*n*=591) with open-label extension, demonstrates long-term efficacy of 50 mg BIW dosing in moderate to severe chronic plaque psoriasis¹⁶. All patients after week 12 were converted to 50 mg BIW therapy. Peak PASI 75 scores were achieved at week 48 with subsequent decline; posthoc analysis showed that the PASI 75 declined by approximately 10% in those with at least 90% compliance. Again, nonneutralizing antietanercept antibodies were found but had no impact on efficacy or safety outcomes. Adverse event rates were similar for the etanercept/etanercept group at 12 and 96 weeks, suggesting extended exposure does not change the drug's toxicity. Nine malignancies and 14 nonmelanoma skin cancers were detected during the study. Although the standardized incidence ratios (SIRs) for these malignancies were not significantly different from age- and sex-matched cohorts from the general population, at least three were considered possibly related to etanercept by the investigator.

TABLE 62-2—TNF Inhibitor Dosing Schedule for Psoriasis

	Adults (FDA label usage)	Children (Off-Label Use)
<i>Etanercept</i>		
- Initiation	50 mg sq twice weekly × 3 months	Psoriasis, Ages 4-17 years
- Maintenance	50 mg sq once weekly	0.8mg/kg (up to maximum 50 mg) once weekly (19, 23) 25 mg or 0.4 mg / kg twice a week (23-25)
<i>Adalimumab</i>		
- Initiation	80 mg sq first dose, 40 mg sq second dose 1 week later	No studies in psoriasis Juvenile Idiopathic Arthritis, ages 4-17 years(8)
- Maintenance	40 mg sq every other	Dosing: 15 to < 30 kg: 20 mg every other week < 30 kg: 40 mg every other week
<i>Infliximab</i>		
- Initiation	5 mg /kg at weeks 0, 2, 6	Case Reports in Psoriasis, Ages 13 and 14
- Maintenance	5 mg/kg every 8 weeks after 3 rd initiation dose; adjust dose and frequency depending upon clinical efficacy and tolerance	3.3 to 5 mg/kg at weeks 0, 2, 6 (26, 27) 3.3 to 5 mg/kg every 8 weeks after 3 rd initiation dose (26, 27) Crohn's Disease (ages 6-17)(7) 5 mg/kg at weeks 0, 2, 6, 10 weeks 5 mg/kg every 8 or 12 weeks

One patient experienced worsened congestive heart failure (CHF).

Dosing of 50 mg once weekly (QW) is supported by a 12 week double-blind, placebo-controlled trial ($n=268$) followed by a 12 week open label conversion study¹⁷.

A large randomized open label study ($n=2546$) demonstrated that etanercept therapy can be interrupted without risk and resumed with good effect¹⁸. Although the continuous group (50 mg BIW followed by 50 mg QW) showed improved outcomes, interrupted therapy subjects were only followed for a maximum of 8 weeks after reinitiation and may have reached similar efficacy if followed over time.

Children and Adolescents

Etanercept use in children with psoriasis has been investigated as well. A 48-week treatment-withdrawal-retreatment study ($n=211$) of etanercept in children and adolescents age 4-17 demonstrated good efficacy¹⁹. Subjects were treated with 0.8 mg/kg etanercept up to 50 mg QW \times 12 weeks initially; 57% of etanercept and 11% of placebo patients achieved PASI 75 at 12 weeks. Weight-based dosing, as opposed to maximum dosage, was considered more effective. Similar to the above retreatment study by Moore et al. efficacy of retreatment in subjects who lost PASI 75 was consistent with response rates seen at similar time intervals during initial treatment phase. Infectious and noninfectious adverse events were similar in placebo and treatment groups. No cancers, deaths, demyelination events, opportunistic infections, or tuberculosis were reported.

Off-Label Indications

HIDRADENITIS SUPPURATIVA

An open-label, uncontrolled Phase II study ($n=10$) evaluated the use of etanercept 50 mg QW for 12 weeks in hidradenitis suppurativa (HS)²⁰. A decrease in fistulas, Sartorius score, visual analog scale, and patient-reported pain was reported. The Sartorius score decreased greater than 50% in six subjects at week 12 and seven subjects at week 24. In contrast, another Phase II study investigating use of etanercept 50 mg QW for HS demonstrated minimal improvement²¹. Quality of life index scores, physician global assessment scores, lesion counts, and patient pain scores showed no difference from baseline at 12 weeks in the latter study. Perhaps higher doses of etanercept will show benefit in the future.

NEUTROPHILIC DERMATOSES

Case reports indicate that etanercept may be helpful in pyoderma gangrenosum, although the more potent TNF-alpha inhibitors infliximab and adalimumab may be more effective¹⁰. Reports also indicate the usefulness of etanercept in Sweet's¹⁰.

GRANULOMATOUS DISEASE

There are limited data, mostly in the form of case reports, to support the use of etanercept in cutaneous sarcoidosis, granuloma annulare, and necrobiosis lipoidica¹⁰.

BULLOUS DISEASE

Case reports have shown benefit for etanercept in mucous membrane and cutaneous pemphigoid, allowing for prednisone tapering in otherwise resistant disease¹⁰.

AUTOIMMUNE CONNECTIVE TISSUE DISEASE

A pilot study of 10 patients with systemic sclerosis treated with etanercept 25 mg BIW for 6 months showed improvement in clinical outcomes, including the Rodnan skin core and digital ulceration¹⁰. Etanercept in a bleomycin-induced murine model of scleroderma showed a reduction in dermal sclerosis, collagen accumulation, and burden of myofibroblastic cells²². Future human studies are required to further substantiate these results. Case reports detailing improvement in dermatomyositis and Behcet's disease have been reported as well¹⁰.

Other reported uses in dermatology for etanercept include acute and chronic graft versus host disease (GVHD), SAPHO syndrome (synovitis, acne, pustulosis, hyperostosis, and osteitis), multicentric reticulohistiocytosis, erythema annulare centrifugum, and Hailey-Hailey disease¹⁰.

INFliximab

Infliximab is a chimeric monoclonal IgG1 antibody that neutralizes TNF-alpha through high affinity binding of soluble and transmembrane forms of TNF-alpha, thus preventing binding of TNF-alpha and its receptor⁷. The constant region of the monoclonal antibody is human, whereas the variable region is murine⁷. Infliximab is FDA approved for the following indications: severe chronic plaque psoriasis, Crohn's disease, ulcerative colitis, psoriatic arthritis, rheumatoid arthritis, and ankylosing spondylitis (See Table 62-1). As with etanercept, the off-label uses are numerous.

Dosing

Infliximab is available only through intravenous infusion. Treatment is performed at outpatient infusion centers. Dosing schedules for psoriasis are listed in Table 62-2.

Efficacy

Psoriasis

A Phase III, double-blind, placebo-controlled study ($n=378$) evaluated the efficacy and safety of infliximab, administered 5 mg/kg at weeks 0, 2, and 6 and then every 8 weeks until

week 46, in moderate to severe plaque psoriasis²⁸. At week 24, the PASI 75 was 82% versus 4% for placebo, but efficacy tapered somewhat with a PASI 75 of 61% at week 50. Nail psoriasis, as measured by the NAPSI score, was also significantly improved as compared to placebo. Anti-infliximab antibodies, which were detected in 19% of subjects at week 66, decreased the efficacy of infliximab. Three serious infections and three hypersensitivity reactions were noted in the treatment group. There were no demyelinating events, tuberculosis or serious opportunistic infections, new onset CHF, or major hematologic events (aplastic anemia, pancytopenia, agranulocytosis).

A study evaluating comparative dosing of 3 mg/kg or 5 mg/kg and continuous versus intermittent dosing showed improved PASI 75 scores with both the 5 mg/kg and continuous groups²⁹. Safety data in this study revealed the following: two cases of tuberculosis, 12 malignancies (10 with nonmelanoma skin cancer who were previously treated with ultraviolet light therapy), elevations in alanine and aspartate aminotransaminases, and two patients with a lupus-like syndrome. No demyelinating events were seen. Anti-infliximab antibodies were correlative with risk of infusion reaction. This study concluded that the ideal dosing regimen was 5 mg/kg administered with an every 8 week maintenance dosing instead of the as-needed regimen.

The impact of infliximab on health-related quality of life (HRQoL) in psoriasis has been evaluated. In a double-blind, randomized, placebo-controlled study (n=835), infliximab (either 3 or 5 mg/kg) was shown to improve Dermatology Life Quality Index (DLQI) and Short-Form Health Survey 36 (SF-36) at 10 weeks. HRQoL correlated with disease severity, the presence of psoriatic arthritis, and depression. Even accounting for these comorbidities, infliximab significantly improved the physical and mental health components of the SF-36 and the DLQI. Similar improvements in the DLQI and SF-36 were noted in another double-blind, randomized, placebo-controlled study evaluating infliximab in chronic plaque psoriasis (REF: 16704649).

There are no prospective studies evaluating the use of infliximab in children and adolescents with psoriasis or psoriatic arthritis. Several cases have been reported supporting the efficacy of infliximab at doses ranging from 3.3 to 5 mg/kg in children with psoriasis³⁰. Infliximab has been used successfully in pediatric Crohn's disease, as evidenced by a Phase III, randomized, open-label study in pediatric subjects with moderate to severe Crohn's disease³¹. Large, prospective, controlled and randomized studies are needed to further assess the efficacy and safety of infliximab in the pediatric population.

Off-Label Indications

GRANULOMATOUS DISEASE

Infliximab has been shown to be one of the most effective antigranuloma medications on the market. The

antigranuloma effect of infliximab has been especially important in the treatment of sarcoidosis. As will be discussed, adalimumab also shows efficacy in granulomatous disease, whereas the evidence for etanercept is less straightforward; perhaps underlying differences in these medications can explain both the increased risk of *Mycobacterium tuberculosis* (TB) reactivation and improved clearance of granulomas with adalimumab and infliximab. Although no prospective studies have been performed, the dramatic responses seen in numerous cases seem to indicate efficacy¹⁰. Cases of successful treatment of granuloma annulare and necrobiosis lipoidica with infliximab have also been reported¹⁰.

HIDRADENITIS SUPPURATIVA

Several case reports and case series document improvement in HS with 5 mg/kg dosing of infliximab¹⁰.

Other disease which have responded to infliximab in the form of case reports or case series include the following: pyoderma gangrenosum, subcorneal pustular dermatosis, Wegner's granulomatosis, dermatomyositis, Behcet's disease, acute and chronic GVHD, pityriasis rubra pilaris, SAPHO syndrome, multicentric reticulohistiocytosis, toxic epidermal necrolysis, and atopic dermatitis^{10,32}.

ADALIMUMAB

Adalimumab is a recombinant fully human monoclonal IgG1 anti-TNF-alpha antibody administered by subcutaneous injection⁸. It is approved by the FDA for the following indications: rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, ankylosing spondylitis, Crohn's disease, and plaque psoriasis (See Table 62-1).

Efficacy

Psoriasis

Like etanercept and infliximab, adalimumab has been shown in several Phase III studies to be effective in the treatment of plaque psoriasis. Although concern about subject selection with respect to extension studies has been raised³³, adalimumab has proven long-term (up to 2 years) efficacy. Several studies have evaluated adalimumab in plaque psoriasis.

A multicenter, randomized, double-blind, placebo-controlled study (n=148) evaluated the safety and efficacy of adalimumab in moderate to severe plaque psoriasis³⁴. After 12 weeks of study receiving either adalimumab 40 mg QW or every other week or placebo, subjects were allowed to continue adalimumab at initial doses or start adalimumab 40 mg every other week. At 12 weeks, 53% and 80% of patients in the every other week and weekly dosing groups, respectively, achieved PASI 75, whereas only 4% of the controls achieved this same level of improvement. Mean PASI improvement continued out to the end of the study,

at 60 weeks. Nine percent of subjects withdrew because of an adverse event. The most common side effects include injection-site reaction, nasopharyngitis, and upper respiratory tract infections. Four malignancies were discovered in the trial in treatment subjects, including two with malignant melanoma, and one each with breast carcinoma and gastric adenocarcinoma. No lymphomas or nonmelanoma skin cancers were detected. One case of pulmonary coccidiomycosis and two cases of TB (one latent, one conversion) were identified. Hepatic transaminases were elevated greater than threefold in two patients and were withdrawn from the study.

Another double-blind, placebo-controlled randomized trial ($n=1212$) investigated adalimumab (40 mg every other week for 15 weeks) in moderate to severe plaque psoriasis³⁵. PASI 75 scores were achieved in 70% of treated patients at 16 weeks compared with only 7% of controls. PASI 75 scores may be elevated because of subject selection bias in that responders were preferentially continued into the open-label portion of the study³³. Six cases of nonmelanoma skin cancer and one case of TB were identified; no cases of lymphoma, demyelinating disease, or lupus were identified.

The safety, efficacy, and impact on quality of life (QOL) of adalimumab was addressed in a double-blind, placebo-controlled randomized-controlled study in a cohort of Japanese patients with moderate to severe plaque psoriasis ($n=169$)³⁶. Similar to the other studies mentioned, PASI 75 scores for the 40 mg every other week groups (one with 80 mg loading dose, and one without) were around 60%. Another group, which received 80 mg every other week, showed a significantly improved 81% PASI 75 at weeks 16 and 24 in comparison to the 40 mg groups. With respect to safety, there were no significant differences in the number of serious adverse events, severe adverse events, or adverse events leading to premature discontinuation of the drug. Differences in injection site reactions and mild elevations in hepatic aminotransferase levels were noted in the treatment groups. Significant improvements in the Dermatology Life Quality Index (DLQI) and the Short Form 36 Health Study (mental and physical components) were noted for all treatment groups.

Children and Adolescents

No studies exist in which children with psoriasis have been treated with adalimumab. Given successful treatment of juvenile idiopathic arthritis with adalimumab, prospective and controlled studies will likely follow.

Off-Label Uses

As with etanercept and infliximab, off-label uses of adalimumab are numerous and growing. Cases of improvement after treatment with adalimumab in sarcoidosis,

pyoderma gangrenosum, multicentric reticulohistiocytosis, dissecting scalp cellulitis, and granuloma annulare have been reported¹⁰⁻¹².

HIDRADENITIS SUPPURATIVA

Six subjects with refractory severe HS were treated with 40 mg every other week adalimumab for 24 months³⁷. The number of affected regions, fistulas, and nodules were reduced significantly at 1 year.

GOLIMUMAB

Golimumab, a novel human IgG1κ monoclonal antibody which specifically targets TNF-α, has been approved by the FDA in the treatment of rheumatoid arthritis, ankylosing spondylitis, and psoriatic arthritis³⁸. The application of golimumab (50 or 100 mg dosed every 4 weeks) for use in psoriasis was partially investigated in a randomized, placebo-controlled, double-blind trial designed to assess its efficacy in a cohort of psoriatic arthritis patients ($n=405$)³⁹. Methotrexate was administered concomitantly. Although the primary outcome was the American College of Rheumatology 20% improvement criteria for arthritis (ACR20), PASI scores were followed in parallel for up to 24 weeks. PASI 75 scores at 14 weeks were 40% and 58% for the 50 and 100 mg doses, respectively; at 24 weeks scores continued to improve in a dose-dependent fashion with PASI 75 obtained by 56% and 66% in the 50 and 100 mg groups, respectively. Importantly, the study population has slightly less severe skin disease with lower affected body surface area and PASI scores than those seen in psoriasis studies, so psoriasis specific trials will help determine the role of golimumab in the dermatologic armamentarium. The most frequent adverse events in the treatment group were nasopharyngitis and respiratory tract infection. No cases of tuberculosis were identified. Three malignancies were discovered during the treatment phase in the 100 mg golimumab group, including two cases of basal cell carcinoma and 1 case of prostate cancer. Anti-golimumab antibodies were detected in 4.6% of patients and had no apparent effect on outcome, although the numbers for detecting a difference were low in the study; no subjects who took methotrexate at baseline developed antibodies.

CERTOLIZUMAB

Certolizumab is a Pegylated Fab' fragment specific for binding TNF-α⁴⁰. Since it lacks an Fc domain, it does not fix complement or cause antibody-dependent cell-mediated cytotoxicity in vitro⁴⁰. The fact that a TNF blocker lacking an Fc component has both efficacy and increased TB reactivation demonstrates that the Fc component does not account for differential safety or efficacy properties among the TNF blockers. Certolizumab does not bind

TABLE 62-3—Pharmacokinetics of TNF Alpha Inhibitors(2, 38, 40)

	Etanercept*	Infliximab	Adalimumab	Golimumab	Certolizumab
Cmax (μg/mL)	1.1 ± 0.6	118 ^{&}	4.7 [^]	2.5	-
Time to Cmax (h)	69 ± 34	NA	131 ± 56 [^]	2-6 days	51-171
Bioavailability	76%	100%	64% [^]	53%	80%
Clearance (mL/h)	160 ± 80	11 ^{&}	12	4.9-6.7 **mL/kg/day	17
Volume of distribution (L)	10.4	3.0	4.7-6.0 [@]	58 – 126 mL/kg ^{**}	6.4
T1/2 (days)	4.25 ± 1.25	8-10 [#]	10-20 [@]	14	14

*25 mg subcutaneous; [&]5mg/kg IV; [#] 3 to 20 mg/kg IV; [^]40mg subcutaneous; [@]0.25 to 10 mg/kg IV; ^{**}0.1-10mg/kg IV; NA – information not available

lymphotoxin A (TNF- β)⁴⁰. Currently, it is approved by the FDA for refractory moderate to severe Crohn's disease in adults. Two studies investigating the use of certolizumab in psoriasis have been completed (Clinical Trials.gov identifiers NCT00329303 and NCT00245765), although published data is lacking currently (clinicaltrials.gov).

PHARMACOKINETICS/ PHARMACODYNAMICS

Table 62-3 demonstrates comparative pharmacokinetic data for etanercept, infliximab, and adalimumab. The half-life of adalimumab is the longest of the three approved TNF inhibitors for psoriasis, allowing for only twice a month injections. Intravenous bolus of infliximab results in high maximum concentration and demonstrates 100% bioavailability (See Table 62-3); these particular pharmacokinetic variables may account for the quick and robust clinical response to infliximab therapy. Golimumab and certolizumab also show long half-lives; they are currently marketed as once-monthly subcutaneous medications. Whether this dosing schedule works in psoriasis is unknown.

With respect to binding avidity, etanercept binds to 2 TNF-alpha subunits in a 1:1 ratio, whereas both adalimumab and infliximab can bind up to two per single drug molecule (2:1 ratio)^{2,41}. It has been suggested that this low ratio allows for safer titration of etanercept than either adalimumab or infliximab, which can effectively neutralize more TNF molecules per unit drug².

SAFETY

Although the risks of therapy vary with each TNF- α inhibitor, the general safety concerns of the drug class include the following: malignancy, susceptibility to infection, demyelinating disease, heart failure, and more common benign side-effects including injection site reactions.

Malignancy

As the field of cancer immunology expands, more will be understood in the complex relationship between cancer

antigenicity and the host response. Currently, immunosurveillance by the host, particularly by natural killer cells, is thought to play a protective role in the body's fight against malignancy⁴². Immunosuppression is considered a risk factor in the development of new malignancies, the most obvious example being the increased risk of melanoma and nonmelanoma skin cancer in solid organ transplant recipients⁴³. To date there are little data which conclusively link the use of TNF- α inhibitors with malignancy. In examining 13,001 patients with rheumatoid arthritis over approximately 49,000 patients years of treatment, Wolfe and Michaud showed that the 49% who received biologics (infliximab, etanercept, adalimumab, and anakinra) had an increased risk of developing nonmelanoma skin cancer (OR 1.9, 95% confidence interval (CI) 1.2-1.8) and possibly increased risk of melanoma (OR 2.3, 95% CI 0.9-5.4)⁴⁴. In this same study, no increases in the rates of hematologic, lung, colon, or breast malignancy were detected. In contrast, a meta-analysis of nine randomized-controlled trials ($n=3,493$) which investigated the use of either infliximab or etanercept for rheumatoid arthritis showed a pooled 3.3 OR (95% CI 1.2-9.1) of malignancy (mostly nonmelanoma skin cancer and lymphoma); higher doses of TNF- α inhibitors was associated with increased odds ratio as well⁴⁵. Large studies in dermatology evaluating the risk of malignancy and TNF- α inhibitor use have not been performed.

Despite lack of conclusive data regarding TNFs and malignancy, the FDA added a black box warning regarding risk of lymphoma and other malignancies in children and adolescents on anti-TNF α therapy⁴⁶. An FDA analysis identified 48 malignancies in children and adolescents on TNF blocker therapy. The reporting rate of lymphoma in the infliximab and etanercept cohorts (adalimumab and golimumab were not assessed for this analysis) was significantly elevated from background; data regarding other TNF blockers was too sparse for further analysis. Additionally, the FDA noted that almost all patients were on concurrent immunosuppressives. Conservative management includes counseling patients about current data and the as of yet unknown risk of neoplasia.

Infection

The use of TNF- α inhibitors is associated with increased risk for infection with *Mycobacterium tuberculosis* (TB)² along with other intracellular infections, including *Histoplasma capsulatum*, *Listeria monocytogenes*, and *Leishmania donovoni*⁹. The FDA released a MedWatch Alert in 2008 concerning the delay in diagnosis and treatment of pulmonary and disseminated infection with histoplasmosis, blastomycosis, and coccidiomycosis in patients on TNF- α inhibitors⁴⁷. The risk for TB infection may be elevated in patients on infliximab and adalimumab in comparison to etanercept². Nonetheless, all patients starting and continuing on TNF- α inhibitor therapy should be screened for TB (see monitoring, below). Furthermore, the risk of serious infections for patients taking infliximab and etanercept for rheumatoid arthritis has been shown to be increased in comparison to placebo patients (OR 2.0, 95% CI 1.3-3.1); similar to risk of malignancy, a dose-response relationship was noted⁴⁵.

Given the increased risk for infection on therapy, vaccination against certain pathogens may be beneficial in certain patients before initiation of anti-TNF- α therapy if possible. Although host immune response against infections is likely blunted, data show that both influenza and pneumococcal vaccines are likely effective during adalimumab therapy⁴⁸. The National Psoriasis Foundation does not explicitly recommend a vaccination protocol, but does recommend vaccination before initiation of anti-TNF- α therapy if the decision has been made to vaccinate⁴⁸. The 2008 American College of Rheumatology (ACR) recommendations for rheumatoid arthritis patients include vaccination with influenza, pneumococcus, and Hepatitis B (if HBV risk factors such as intravenous drug use, multiple sexual partners in the previous 6 months, health care worker are present) vaccines⁴⁹. Both groups recommend against the use of live vaccines in these patients.

The use of TNF inhibitors in patients with certain existing viral and bacterial (mycobacterial) infections should be avoided or done so cautiously. Reactivation of HBV has been noted in patients on infliximab and adalimumab but not etanercept⁵⁰⁻⁵². Although chronic HBV infection is not an absolute contraindication to TNF inhibitor therapy, careful monitoring of liver function tests and HBV DNA levels is a must; pretreatment with appropriate antivirals may prevent reactivation, although data is limited^{50,53}.

Whereas TNF has been shown to control viral replication in HBV, TNF does not seem to play as significant a role in controlling HCV⁵⁰. One case series of HCV-infected RA patients ($n=31$) treated with etanercept, infliximab, and adalimumab supports the use of anti-TNFs in HCV-infected patients provided liver enzymes and HCV viral loads are monitored regularly⁵⁴. In this study, four patients experienced elevation in viral load without hepatotoxicity and one patient discontinued anti-TNF use because of persistently elevated alanine aminotransferase

without viral load elevation. A recent consensus paper by the National Psoriasis Foundation recommends TNF inhibitors, particularly etanercept, along with PUVA and other systemics like acitretin as a second line medication for patients with HCV⁵⁵. Magliocco and Gottlieb reported three patients with psoriasis, psoriatic arthritis, and HCV who were successfully treated with etanercept without a worsening in their liver function or viral load⁵⁶. In fact, a Phase II randomized, placebo-controlled trial ($n=50$) indicates that adjuvant etanercept use in combination with interferon and ribavirin for chronic hepatitis C may help establish virologic clearance and normalize hepatic transaminases; furthermore, etanercept recipients experienced fewer or equivalent side effects for nearly all adverse effects⁵⁷.

Demyelinating Disease

Case reports indicate that anti-TNF- α therapy can initiate or uncover underlying demyelinating disease. The following peripheral nerve disorders have been reported with anti-TNF- α therapy: Guillain-Barré syndrome, Miller Fisher syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy with conduction block, mononeuropathy multiplex, and axonal sensorimotor polyneuropathies⁵⁸. Nonetheless, some authors have indicated the incidence of demyelinating disease is not elevated during anti-TNF- α therapy⁵⁹. If a strong family history of multiple sclerosis or other demyelinating disease is present, it may be best to avoid anti-TNF- α therapy until this risk is further characterized. Cessation of anti-TNF- α therapy is generally regarded as the best approach toward treatment, although some have more recently advocated that stopping the withdrawal is not always necessary for neuropathy control⁶⁰.

Hepatotoxicity

Elevations in serum aspartate and alanine aminotransaminase (AST and ALT), which are usually but not always reversible, have been reported with TNF-inhibitors, particularly infliximab^{9,48}. Although the sequelae of such elevations is unclear, the medical board of the National Psoriasis Foundation has recommended withholding treatment if either the AST or ALT is equal to or greater than five times the normal limit⁴⁸. It may also prudent to recheck serologies for hepatitis B in previously exposed patients. HBV reactivation has been reported in patients with antibodies to both hepatitis core and surface antigens (HBsAb and HBcAb) with negative HBsAG (surface antigen)⁵⁰.

Hematologic Toxicity

Rarely, the following hematologic side effects have been noted with the anti-TNF- α agents: anemia, leukopenia, neutropenia, thrombocytopenia, pancytopenia, and

aplastic anemia⁴⁸. Although infrequent, monitoring the CBC regularly throughout treatment is sensible (see monitoring, below).

Heart Failure

New onset or worsening of existing congestive heart failure (New York Heart Association Class III-IV) leading to death and hospitalization has been noted at high doses of infliximab (10 mg/kg)⁷. The package inserts for all five TNF inhibitors warn patients of these risks^{6-8,38,40}.

Infusion Reactions: Infliximab

Of all the TNF-inhibitors, infliximab is the only one administered intravenously. Infusion-related hypersensitivity reactions, including hypotension, urticaria, and/or dyspnea may occur, most commonly during or within first 2 hours of treatment⁷. Emergency treatment for hypersensitivity reactions, including appropriate staff and medications, should be readily accessible in infusions centers.

Delayed infusion reactions have been reported, particularly when infliximab is readministered in patients who have developed anti-infliximab antibodies and the interval between restarting therapy and the previous dose was 6 months or longer⁷. Most of these reactions were noted in a cohort of Crohn's patients upon reinitiation of infusions; 3 to 12 days after infusion, affected patients experienced myalgia and/or arthralgia, fever, rash, facial, hand, or lip edema, dysphagia, urticaria, sore throat, and headache⁷.

Injection site reactions: Etanercept, Adalimumab, Certolizumab, Golimumab

The most common side effect of the injectable anti-TNF agents is an injection site reaction, defined as redness, swelling, itching, or bruising at the site of injection. Approximately 15 - 20% (adalimumab 19%; etanercept 14%) of subjects in trials have experienced injection site reactions. Generally the reactions are mild to moderate, lasting about 3-5 days with decreasing frequency over time⁶.

MONITORING

A consensus statement from the Medical Board of the National Psoriasis Foundation addresses appropriate laboratory monitoring when initiating biologics in psoriasis⁴⁸. Appropriate laboratory tests at baseline include complete blood count (CBC) with platelet count, liver function tests (including serum alanine and aspartate aminotransaminases), hepatitis B and C panels, and a tuberculin skin test (PPD) or other appropriate screening test for tuberculosis. The frequency of monitoring varies, although checking a CBC and LFTs every 3 months may be appropriate given

reports of leukopenia, neutropenia, pancytopenia, and fatal hepatitis⁷. Drug induced thrombocytopenia has also been noted with TNF-alpha inhibitor therapy^{7,61}. If bruising or excessive bleeding is noted on therapy, prompt evaluation of a CBC with platelet count is indicated.

A consensus group published guidelines in 2008 regarding TB and biologics in dermatology⁶². First, all patients should be screened for TB risk before initiating immunosuppressive therapy. Second, screening should commence yearly after initiation of TNF-alpha inhibitors given the increased risk of reaction. Third, a 5 mm or greater induration in a tuberculin skin test should be considered positive in immunosuppressed patients. Fourth, if a patient is found to have latent TB, immunologic therapy can be started 1 to 2 months after initiating therapy with isoniazid, although the preference is to complete full course of therapy before starting the biologic. Finally, active TB must be treated with a full four-drug regimen before initiating biologic therapy.

KEYS TO PRESCRIBING

Neutralizing autoantibodies have been detected in the following TNF-inhibitors: infliximab, adalimumab, certolizumab, and golimumab^{7,8,38,40}. The level of antibody production varies according to the particular drug, disease indication, and length of therapy. The prevalence of antidirug antibodies is lowered with concomitant use of methotrexate. Because of the development of neutralizing antibodies, restarting the same TNF-inhibitor after cessation of previous therapy may lead to higher drug failure rates; thus, reinitiating therapy with another agent may be more beneficial. Alternatively, starting the TNF-inhibitor once the patient is already on a stable dose of methotrexate can reduce the development of neutralizing antibodies and may lower long-term treatment failures. Efficacy over the long term may be reduced secondary to development of neutralizing antibodies.

TNF-flared psoriasis has been reported in patients taking anti-TNFs for psoriasis (plaque, pustular, erythrodermic), ankylosing spondylitis, rheumatoid arthritis, inflammatory bowel disease, and Behcet's disease⁶³. A recent review of TNF-induced psoriasis identified infliximab as the culprit agent in the majority of cases (55.1%) followed by etanercept (27.6%) and adalimumab (17.3%)⁶⁴. Most patients were being treated for rheumatoid arthritis (50.4%) followed by ankylosing spondylitis (16.1%), Crohn's disease (13%), psoriasis (6.9%), psoriatic arthritis (3.1%), ulcerative colitis (1.5%), and Behcet's disease (6.9%)⁶⁴. In this review, palmar-plantar eruptions were the predominant morphology identified (40.5%), followed by plaque (33.1%), and guttate (10.2%). The time interval between starting the TNF-inhibitor and the onset of the psoriasisform eruption has ranged from 15 days to 20 months⁶³. This phenomenon is a class effect; switching to another TNF blocker is unlikely to resolve the flare.

The most effective management is to stop the TNF blocker and initiate an alternative systemic therapy⁶⁴.

Patients should be free from severe illness or infection when initiating therapy. If a patient experiences severe illness or infection while on therapy already, skipping the next dose—if in close proximity to illness—is prudent.

Drug-induced lupus has been reported with TNF-inhibitors. Although the development of autoantibodies (ANA and dsDNA) is relatively common during therapy, drug-induced lupus (DIL) is not⁶⁵. When it occurs, anti-TNF-induced lupus (ATIL) presents differently than classic cases of DIL. ATIL presents more like classic systemic lupus erythematosus with serositis, myositis, nephritis, CNS involvement, cutaneous eruptions, and positive anti-nuclear and anti-dsDNA antibodies than DIL. Antihistone antibodies may be present, but are not present nearly as often as in DIL⁶⁵.

USTEKINUMAB: IL-12/23 INHIBITORS

Greater understanding of the pathogenesis of psoriasis, psoriatic arthritis and the recently characterized Th17 cell has led to the development of the IL-12/23 inhibitor ustekinumab⁶⁶. Ustekinumab is a human IgG1 antibody, which specifically targets the shared p40 subunit of IL-12 and IL-23⁶⁷. Although it has not yet been approved by the US FDA (as of this writing), ustekinumab (also known as CANTO 1275) has been studied in psoriasis, psoriatic arthritis, Crohn's disease, and multiple sclerosis^{68–72}.

Efficacy

Psoriasis

The safety and efficacy of ustekinumab for use in moderate to severe plaque psoriasis was evaluated in the PHEONIX 1 trial, a Phase III, double-blind, randomized, placebo-controlled, multicenter study ($n=766$)⁷³. Approximately half of the subjects had tried biologics (TNF inhibitors) before the study. Subjects received either 45 or 90 mg of ustekinumab at weeks 0, 4, and then every 12 weeks; placebo patients underwent crossover after the first two placebo doses (weeks 0 and 4) with subsequent treatment with either 45 or 90 mg of ustekinumab. At 12 and 28 weeks, 67.1% and 71.2%, respectively, of the 45 mg group reached PASI 75; the 90 mg group showed similar response at week 12 (66.4%) and, like the 45 mg group, continued to improve at week 28 (78.6%). The PHEONIX 2 study, also a multicenter, randomized, placebo-controlled, Phase III study evaluating the use of ustekinumab in moderate to severe plaque psoriasis, showed very similar results to PHEONIX 1⁷⁴.

Follow-up studies for both PHEONIX 1 and 2 evaluated how ustekinumab treatment affects health-related quality of life (HRQoL) in psoriasis. In the PHEONIX 1 study, HRQoL was assessed by the DLQI (Dermatology Life

Quality Index) and SF-36 tools. Significant improvements in both the DLQI and SF-36 were noted at week 12 in the ustekinumab groups and were sustained at least through 1 year of maintenance therapy. Interestingly the improvements in SF-36 were no longer significant if adjusted for PASI and physicians general assessment (PGA) scores, which may indicate how directly quality of life in psoriasis is impacted by the physical manifestations of disease. In the PHEONIX 2 study, the Hospital Anxiety and Depression Scale in addition to the DLQI were evaluated. Similar to the PHEONIX 1 data, the DLQI outcomes in PHEONIX 2 showed significant improvement at week 12 compared to placebo and correlated well with PASI scores. At 12 weeks, a smaller proportion of ustekinumab-treated subjects experienced symptoms of mild to severe anxiety and depression versus baseline, whereas the placebo groups demonstrated an increase over the same time interval.

A head to head comparison trial of ustekinumab versus etanercept for the treatment of moderate to severe plaque psoriasis ($n=903$) demonstrated improved PASI 75 and PGA scores over a 12 week period. In this multicenter, investigator-only blinded study, subjects were randomized to receive either ustekinumab (45 or 90 mg monthly injections) or high-dose etanercept (50 mg twice weekly) for 12 weeks. At week 12, PASI 75 scores for ustekinumab 45 mg, ustekinumab 90 mg, and etanercept were 67.5, 73.8, and 56.8%, respectively. The percentage of subjects achieving PGA scores of clear or minimal disease at week 12 for these respective groups, were 65.1%, 70.6%, and 49%. After 12 weeks, the etanercept group was crossed-over to receive higher-dose (90 mg monthly) ustekinumab. Of the etanercept nonresponders at 12 weeks (PGA ≥ 3), 48.9% achieved PASI 75 after cross-over to 90 mg monthly ustekinumab.

In addition to psoriasis, ustekinumab has been shown to effectively treat psoriatic arthritis in a Phase II multi-site, double-blind, placebo-controlled, randomized cross-over study ($n=146$)⁷². At 12 weeks, 42% of subjects treated with either 90 mg or 63 mg of ustekinumab weekly for 4 weeks achieved the ACR20, whereas only 14% of the placebo-treated group reached this same cut-off. Furthermore, the improvement in joint disease was durable in that about three-quarters of those who met ACR20 at week 12 still met these criteria at 36 weeks, 33 weeks after the last ustekinumab injection. In addition to the arthritis outcomes, significant improvements in PASI 75 and DLQI scores were also noted in the treatment group at 12 weeks.

Safety

The most commonly reported adverse events in the PHEONIX 1 and 2 studies include the following: respiratory tract infection, nasopharyngitis, headache, and arthralgia. Several serious infections were reported in the treatment groups (herpes zoster, lower extremity cellulitis, "viral

syndrome", osteomyelitis in a diabetic with a foot ulcer, gastroenteritis, appendicitis, and diverticulitis). No significant laboratory abnormalities were noted. Several new malignancies were noted during the study period, including lentigo maligna, breast cancer, transitional cell carcinoma, prostate, thyroid, colon cancer, squamous cell carcinoma of the tongue. Cardiac disorders, including angina and coronary artery disease, were also included in the list of serious adverse events reported. Antibodies to ustekinumab developed in approximately 5% of patients by week 76.

A double-blind, randomized, placebo controlled, cross-over study investigated the use of ustekinumab in psoriatic arthritis ($n=146$)⁽⁷²⁾. Safety data from this study indicates that infections and striking abnormalities in hematologic and chemistry tests were similar in the placebo and drug treatment groups up to week 12. Several serious adverse events in ustekinumab treated subjects were reported: syncope, respiratory-tract infection, hemorrhage, stroke, congestive heart failure/myocardial infarction/hypertension, chest pain, gastric ulcer hemorrhage, and abdominal pain/back pain.

ALEFACEPT: LFA-3/CD-2 T-CELL ACTIVATION

Alefacept is a human LFA-3 fusion protein which inhibits antigen-presenting cell-T-cell interactions and causes antibody-dependent T-cell cytotoxicity^{66,75}. This dimeric fusion protein consists of the extracellular CD-2-binding portion of LFA-3 (leukocyte function antigen-3) linked to the Fc portion of human IgG1⁷⁵. By binding to CD2 on T cells, alefacept blocks the costimulatory signal for CD45RO+ memory effector T cell activation. Activated T cells populations are depleted as well because the Fc portion of alefacept enables natural killer cell recognition (via the FcR).

Dosing

Although alefacept has been evaluated both for intravenous and intramuscular (IM) administration, current product labeling recommends once weekly IM injections for 12 consecutive weeks⁷⁵. A repeat course can be administered, provided T-cell counts are stable and the medication is otherwise being tolerated.

Efficacy

The main dermatologic use of alefacept is for psoriasis.

Psoriasis

Alefacept was the first biologic drug treatment developed specifically for a dermatologic disease⁶⁶. Alefacept and efalizumab (withdrawn from the US market because of safety concerns) were designed to specifically affect the T-cell

arm of psoriasis pathogenesis. Efficacy in comparison to the TNF inhibitors is likely reduced, although long-term comparisons are difficult to make because of study design and preferential short-term follow-up³³. A multicenter, Phase III, placebo-controlled, randomized, double-blind study investigating the use of IM alefacept (either 10 mg or 15 mg once weekly for 12 consecutive weeks), demonstrated efficacy in moderate to severe chronic plaque psoriasis ($n=507$)⁷⁶. PASI scores continued to improve after the 12-week treatment phase, likely a result of prolonged pathogenic T-cell depletion. Throughout this study, 33% and 28% of the 15 mg and 10 mg groups, respectively, achieved PASI 75.

The combination of narrow band UVB and alefacept for psoriasis has been promoted in several studies⁷⁷⁻⁷⁹. Nonetheless, the added value of nbUVB cannot properly be assessed given the lack of large properly controlled studies.

Alefacept has also been evaluated for palmoplantar pustular (30 mg/week)⁽⁸⁰⁾, scalp⁸¹, and nail⁸² psoriasis. Despite reported improvements, these were open-label, uncontrolled studies; more rigorous studies are required before definitive claims of efficacy can be made. Other off-label uses include alopecia areata and lichen planus⁸³.

Other Diseases

Pyoderma Gangrenosum has also been reported to respond to alefacept in one open-label study⁸⁴. A double-blind, randomized, placebo-controlled study ($n=45$) demonstrated no efficacy for alefacept in the treatment of chronic and severe alopecia areata for more than 12 weeks.

Safety

A pooled analysis of 13 alefacept trials ($n=1869$, 2589 person-years of treatment) characterized the most likely side effects, which include the following: headache, upper respiratory tract infection, influenza, and pruritus⁸⁵. In this same analysis, no cases of opportunistic infection, tuberculosis, or deaths related to infection were reported. Similar to the rate of serious infections, the malignancy risk does not appear to be elevated beyond baseline⁸⁶. One of the major considerations of therapy is the risk of dose-dependent reductions in circulating CD4+ and CD8+ T-cells during therapy⁷⁵. The product insert recommends checking T-cell counts every 2 weeks during the treatment stage and withholding further treatment if the CD4+ T-cell count drops below 250 cells/ μ L. Nonetheless, in the systemic review by Goffe et al. the infection rate did not correlate with reduced circulating CD4+ T-cells⁸⁵).

ANTI-B-CELL THERAPIES

Rituximab is a CD-20 specific monoclonal humanized antibody which targets pre-B and mature B lymphocytes⁸⁷. It is

currently approved by the US FDA for treatment of rheumatoid arthritis and Non-Hodgkin's Lymphoma (NHL), but it has been used in a variety of dermatologic conditions⁸⁸. Nonetheless, no randomized, double-blind studies of rituximab exist for these off-label uses.

Dosing

Rituximab is administered as an intravenous infusion. The off-label uses of rituximab in dermatology have generally followed the NHL dosing, which is 375 mg/m². The frequency and duration of treatment varies widely. The approved dosing for rheumatoid arthritis is two separate 1000 mg infusions administered 2 weeks apart in combination with methotrexate. The initial infusion rate is generally initiated at 50 mg/hour. If the patient is tolerating the infusion well, the rate can be increased 50 mg/hour each 30 minutes up to a maximum of 400 mg/hour. Subsequent infusions can initiate and proceed at faster rates⁸⁷.

Efficacy

The most well studied off-label dermatologic uses of rituximab include the treatment of pemphigus vulgaris (PV) and other autoimmune blistering diseases.

Despite the lack of rigorously controlled large studies, it is evident that rituximab can improve PV and even induce long-lasting remissions. Several different treatment algorithms have been proposed in treating PV. Ahmed et al. published a series of 11 patients with pemphigus vulgaris with greater than 30% body surface area involvement⁸⁹. Patients were initially administered 2 cycles of rituximab (375 mg/m²) once a week for 3 weeks along with intravenous globulin (IVIG, 2 g/kg) on the fourth week; once monthly IVIG and rituximab was then administered for the 4 subsequent months. Sustained remission was noted in 9 of 11 patients with a mean of 31.1 months. Anti-desmoglein autoantibodies decreased after rituximab therapy in the nine patients with durable response, an important finding which has been repeated in other studies as well⁹⁰. Deletion of autoreactive B cells with subsequent down-regulation of desmoglein-specific CD4+ T-cells has been implicated in the ultimate response to therapy⁹⁰. Another study by Joly et al. reported the use of once weekly rituximab (375 mg/m²) for 4 consecutive weeks in 21 patients; 18 patients (86%) were disease-free at 34 months, eight of whom were weaned completely from corticosteroids⁹¹.

Good clinical outcomes have been reported in pemphigus foliaceus, paraneoplastic pemphigus, bullous pemphigoid, and epidermolysis bullosa acquisita (EBA); importantly, several deaths from severe bacterial, viral, and fungal infections have been reported in these patient populations⁹². A recent review of 71 patients with PV, pemphigus vegetans, EBA, paraneoplastic pemphigus, pemphigus foliaceus, and combined bullous pemphigoid and GVHD

showed complete or partial response to rituximab in 94% of patients⁹³.

Numerous studies report marked improvement, including clearance, of primary cutaneous B-cell lymphoma after treatment with rituximab^{94,95}. The European Organization for Research and Treatment of Cancer and the International Society for Cutaneous Lymphoma consensus recommendations for management of cutaneous B-cell lymphomas includes rituximab (intravenous and intralesional) as first line treatment option for primary cutaneous follicular cell lymphoma and diffuse large cell lymphoma, leg type, particularly if the patient has very extensive skin lesions⁹⁶.

Several retrospective and prospective case series published support the use of rituximab in steroid-refractory chronic graft versus host disease⁹⁷. Small studies or case reports show improvement with rituximab in atopic dermatitis ($n=6$)⁹⁸, cutaneous lupus erythematosus (including SCLE⁹⁹, lupus profundus¹⁰⁰, and cutaneous manifestations of SLE¹⁰¹), and cutaneous vasculitis¹⁰². Although case reports show benefit of treating dermatomyositis with rituximab, an open label trial evaluating both muscle and skin symptoms ($n=8$) showed no significant difference in outcomes at 24 weeks¹⁰³.

Safety

Most reported safety data for rituximab pertains to patients treated for systemic lymphoma, either as mono- or combination therapy. In non-Hodgkin lymphoma (NHL) patients, the most common adverse reaction is the infusion reaction. A type-1 hypersensitivity-like reaction including hypotension, urticaria, and bronchospasm may occur within the first 30 to 120 minutes of treatment; supportive measures and either slowed or interrupted infusion is recommended⁸⁷. Similar reactions have been seen in rheumatoid arthritis (RA) patients as well. Serious infections may occur at increased frequency during treatment. Although these occurred fewer than 5% and 2% in NHL and RA patients, respectively, signs, and symptoms of infection should be sought out and managed proactively⁸⁷. A review of pemphigus patients treated with rituximab also indicated an increased risk of infection during treatment, although many were prescribed additional immunosuppressants⁹². A separate review of 71 patients with autoimmune blistering disease identified six patient deaths, four of whom were treated for paraneoplastic pemphigus, one with PV, and another with a combination of bullous pemphigoid and GVHD; most of these deaths were attributed to sepsis, congestive heart failure, or pneumonia⁹³.

A major concern of rituximab remains the potential risk of developing progressive multifocal leukoencephalopathy (PML), a deadly brain infection caused by the JC virus. Although causation remains unproven, the US FDA has issued several warnings regarding the risk of infection and death¹⁰⁴. Physicians supervising therapy with rituximab should monitor for progressive and gradual

impairments in speech, vision, motor function, and overall cognition¹⁰⁴.

Intravenous immunoglobulin (IVIG) coadministration, in addition to facilitating disease improvement, may also be necessary to help reduce infectious complications⁹². In the previously mentioned review of 71 patients treated with rituximab for autoimmune blistering disease, none of the six who died were treated with concomitant IVIG⁹³.

INTRAVENOUS IMMUNOGLOBULIN

Intravenous immunoglobulin, comprised of pooled polyclonal IgG derived from the human blood donor serum, is not approved for any dermatologic condition. Nonetheless, it has been used off-label in a variety of disorders. Despite the use in dermatology and other disciplines of medicine, its precise mechanism of action is unknown; potential mechanisms providing benefit in autoimmune and other disease is discussed in a recent review¹⁰⁵.

Efficacy

Autoimmune Diseases

Interestingly, IVIG works well in the short-term management of autoantibody diseases including autoimmune blistering disease and the ANCA vasculitides. As discussed above, IVIG has been shown to work well, in conjunction with rituximab, in the treatment of pemphigus vulgaris. A recently completed randomized, double-blind, placebo-controlled study evaluated the treatment with one cycle of IVIG in patients with either pemphigus vulgaris or foliaceus ($n=61$)¹⁰⁶. At baseline, patients were unable to lower the oral daily prednisone dose below 20 mg and 10-35% of patients were on concomitant immunosuppressants. The time to escape from protocol (defined as increasing the steroid dose or supplementation with another immunosuppressant) was significantly longer in the 400 mg/kg/day group than placebo. Pemphigus activity scores and IgG autoantibody titers to desmoglein 1 and 3 were lower after 85 days of follow-up in both treatment groups (200 or 400 mg/kg/day \times 5 days). Given the short follow-up, long-term outcomes are unclear. This data is further supported by the initial work of Ahmed, who reported the use of successive cycles of IVIG in patients with oral and cutaneous pemphigus vulgaris and foliaceus^{107,108}.

Successful treatment of other autoimmune blistering disorders with IVIG, including bullous pemphigoid (BP), have also been reported¹⁰⁹. In this study, 15 subjects with refractory severe BP were prospectively treated with repeated cycles of 2 g/kg IVIG. The interval between cycles was set at 4 weeks initially and spaced out to 16 weeks before termination of therapy (upon clearance). The total number of cycles ranged from 10 to 18. After discontinuing IVIG therapy, patients were followed for a mean of 20 months without relapse or recurrence of pemphigus or serious long-term side effects from IVIG.

Vasculitis

Intravenous immunoglobulin is beneficial in the short-term management of various autoantibody driven diseases. Limited data support the use of IVIG in ANCA vasculitis, including Wegner's, microscopic polyangiitis, and Churg-Strauss. Good data, including randomized-controlled trials, indicate that IVIG can eliminate fever in the vast majority of patients with Kawasaki disease and reduces the risk of coronary artery aneurysm¹¹⁰.

Although a mortality benefit was previously described in high-dose IVIG-treated toxic epidermal necrolysis (TEN) patients, subsequent data are inconclusive. An initial noncontrolled, retrospective, multicenter study of IVIG in TEN showed a mortality of only 12%¹¹¹. The proposed mechanism of action is that IVIG blocks Fas-Fas-ligand-induced epidermal apoptosis cascade. A retrospective analysis of 281 patients with Stevens-Johnson syndrome/TEN was completed as part of the EuroSCAR study¹¹². Neither IVIG nor corticosteroids were found to have any mortality benefit.

Safety

Thromboembolic complications, including deep venous thrombosis, myocardial infarction, and ischemic stroke, may occur in up to 13% of IVIG-treated patients¹¹³. Renal insufficiency, aseptic meningitis, congestive heart failure, and hemolytic anemia, may be induced as well with therapy^{9,114,115}. IgA-deficient individuals who produce anti-IgA antibodies may experience anaphylaxis when administered IVIG¹¹⁴. Serum immunoglobulin classes should be evaluated in advance of treatment to safeguard against this life-threatening complication. Patients should also be prescreened for infectious hepatitis and HIV. Baseline evaluation including renal and liver function tests, complete blood count, rheumatoid factor, and cryoglobulins is also recommended¹¹⁴.

DENILEUKIN DIFTITOX

Denileukin diftitox is a recombinant fusion protein, which combines active diphtheria toxin with the membrane translocation domain of IL-2¹¹⁶. Cells that express the IL-2 receptor are selectively targeted for cell death. Denileukin diftitox is approved by the FDA for the treatment of persistent or refractory cutaneous T-cell lymphoma (CTCL) whose malignant cells express the CD-25 component of the IL-2 receptor¹¹⁷.

Efficacy

Denileukin diftitox was assessed in a Phase III study ($n=71$) for the treatment of stage Ib-III CTCL (Cooperative Group Staging; patients with greater than 10% body surface area excluding visceral involvement). Subjects had failed at least

one prior therapy and at least 20% of lymphocytes in the skin had to stain positively for CD-25 on immunohistochemistry. The study dosing included two randomized groups of 9 or 18 µg/kg/d and administered for 5 consecutive days approximately every 3 weeks. Thirty percent of subjects experienced subjective response and 10% achieved either complete pathologic or clinical response.

Safety

Denileukin diftitox is administered through intravenous infusion. Approved dosing is 9 or 18 mcg/kg/day over 30 to 60 minutes for 5 continuous days every 3 weeks for 8 total cycles¹¹⁷. Infusion reactions, including fever, nausea, rigors, vomiting, diarrhea, and pruritus, occur commonly, especially during the initial two infusions; rare post-marketing reports of death after infusion have been reported. Capillary leak syndrome may occur at any point during therapy and has been reported to occur in up to 32.5% of patients. To reduce likelihood of developing capillary leak syndrome, serum albumin levels should be monitored and treatment withheld if lower than 3 g/dL. Loss of visual acuity and color vision has been reported as well.

ABATACEPT

Abatacept is a soluble fusion protein, which inhibits T-cell costimulation. This protein links the extracellular domain of CTLA-4 (cytotoxic T-lymphocyte-associated antigen 4) with a modified Fc portion of human IgG1. The CTLA-4 region binds CD80 (B7-1) and CD86 (B7-2) on antigen presenting cells, thus blocking the CD28 driven co-stimulatory activation of T-cells¹¹⁸. Abatacept is approved for juvenile idiopathic arthritis and rheumatoid arthritis. Limited data support the use of abatacept in psoriasis.

Efficacy

A Phase I dose-escalation study evaluating the use of abatacept in a cohort of chronic plaque psoriasis in patients ($n=43$) with 10-49% body surface area has been conducted¹¹⁹. One hour infusions were given on days 1 and 3 and then at weeks 3 and 5, with doses ranging from 0.5 to 50 mg/kg. Forty six percent of subjects demonstrated a 50% or greater improvement in their Physician's Global Assessment of disease activity.

Safety

Abatacept is administered as an intravenous infusion. As with other infusions, hypersensitivity, anaphylaxis, and anaphylactoid reactions may rarely occur¹¹⁸. Coadministration with a TNF-inhibitor may increase the risk for infection and should be avoided. Pretreatment screening for TB is recommended. Avoidance of live

vaccines is recommended during treatment and up to 3 months after discontinuation. The rates of both lung cancer and lymphoma may be elevated in patients who undergo therapy with abatacept¹¹⁸. In the Phase I study of psoriasis patients mentioned above, the most common adverse events were uncomplicated respiratory tract infection (16%) and transient headache (16%)¹¹⁹.

OMALIZUMAB

Omalizumab is a humanized monoclonal IgG1κ antibody which binds to human IgE¹²⁰. Treatment can lower IgE levels and prevent IgE-mediated inflammatory pathways, including mast and basophil cell activation¹⁰. It is currently approved by the US Food and Drug Administration for treatment of moderate to severe persistent asthma. Approved dosing is 150 to 375 mg administered subcutaneously every 2 to 4 weeks¹²⁰.

Efficacy

Several case series have evaluated the use of omalizumab in atopic dermatitis¹⁰. One study of 3 adults with severe atopic dermatitis treated with omalizumab showed no improvement after twice monthly injection of 450 mg for 4 months¹²¹. In contrast, 100% (3/3) of pediatric patients with atopic dermatitis showed improvement during treatment at doses up to 450 mg every other week¹²². Importantly, these children were all shown to have positive radioallergosorbent testing reaction to aeroallergens; none of the three adults in the former study were demonstrated to have positive radioallergosorbent testing. Furthermore, treatment in the pediatric study was supplemented by topical corticosteroids, topical calcineurin inhibitors, oral mast cell stabilizers, and oral antihistamines. More rigorous studies are required before omalizumab therapy can be recommended for atopic dermatitis.

Improvement in a patient with solar urticaria and another with cholinergic urticaria has been reported after treatment with omalizumab^{123,124}. Clinical trials are ongoing to evaluate the use of omalizumab in bullous pemphigoid and chronic idiopathic urticaria¹²⁵.

Safety

Anaphylaxis, in some cases life-threatening, has been reported after administration of omalizumab in up to 0.2% of patients (based on postmarketing surveillance)¹²⁰. Otherwise, omalizumab appears to be a relatively safe and well-tolerated drug. The most commonly reported adverse events include injection site reactions (45%), viral infections (23%), upper respiratory tract infection (20%), sinusitis (16%), headache (15%), and pharyngitis (11%)¹²⁰. Malignant neoplasms have been observed in 0.5% of omalizumab patients compared with 0.2% of controls in studies of asthma or allergic disorder patients¹²⁰.

What We Know

- Biologic medications are an increasingly important and powerful treatment option in dermatology.
- Biologics for psoriasis offer the hope for safe and effective long-term maintenance of clearance.
- Data support the off-label use of TNF-alpha inhibitors in a variety of dermatoses, including hidradenitis suppurativa, granulomatous diseases, and neutrophilic disorders.
- Biologics blocking IL-12/IL-23 are highly effective in psoriasis and may also be effective in psoriatic arthritis.
- Rituximab/IVIG are useful in recalcitrant autoimmune blistering disorders.
- Biologics may be useful in the treatment of cutaneous lymphoma, systemic and cutaneous vasculitis, severe refractory atopic dermatitis, and many other disease entities.

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Topical Immunomodulators

63

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INTRODUCTION

The advent of new topical agents such as topical calcineurin inhibitors (TCIs) has broadened the range of drugs available to dermatologic diseases. This increase in therapeutic choices offers clinicians an array of more physiologic pathways and mechanisms of action through which treatment can be accomplished and more options for combination therapies. The most rational approach to utilize when deciding which agents to combine in a multidrug regimen is to consider the mechanisms of action of the drug categories commonly used to treat skin disease. These classes include topical corticosteroids, vitamin D₃ analogs, Retinoids, and TCIs. In this chapter, we will cover topical immunomodulator, focusing in particular on the most commonly used ones: tacrolimus and pimecrolimus; sirolimus will be mentioned too.

The US Food and Drug Administration (FDA) approved pimecrolimus in December 2001 as a short-term and intermittent long-term therapy for mild to moderate atopic dermatitis. In January 2006, the prescribing information and indication were revised because of the report of cases of skin malignancy in patients using pimecrolimus cream 1. Nowadays pimecrolimus is indicated as second-line therapy for the short-term and noncontinuous chronic treatment of mild to moderate atopic dermatitis in adults and children aged 2+ years who do not respond to other treatments or for those for whom the use of those treatments is not advisable¹.

Tacrolimus, initially named FK506², was isolated in 1987 from a product of *Streptomyces tsukubaensis*. It is a macrolide lactone produced for the prevention of organ rejection after an allogenic liver or kidney transplant. Topical tacrolimus was introduced in 1999 in Japan, and then in the United States in December 2000 for the short-term and noncontinuous treatment of moderate to severe atopic dermatitis. In March 2005, the FDA issued an alert to health care professionals, advising them to use tacrolimus as well as pimecrolimus, only as directed and only after other eczema treatments had failed, because of possible cancer risk.³

Sirolimus, also known as rapamycin⁴, is a macrocyclic lactone produced by the organism *Streptomyces hygroscopicus*. It was originally identified as an antifungal agent but was later found to have potent immunosuppressive

activity. For this reason, it was initially used as an immunosuppressive drug in transplant patients. Sirolimus shares a homology with tacrolimus, and acts through the specific binding of a family of cytosolic immunophilins known as FK-binding proteins (FKBP). However, the sirolimus-FKBP complex does not act on the nuclear factor of activated T cells or on calcineurin in the manner of tacrolimus⁵.

MECHANISM OF ACTION AND PHARMACOKINETICS

The actions of Tacrolimus and Pimecrolimus likely are similar (Table 63-1). They are both complex macrocyclic compounds that bind to the intracellular protein macrophilin-12 (FK506-binding proteins) and function as macrolactam immunomodulators, thereby inhibiting the activity of the calcineurin.

The therapeutic effects of tacrolimus and pimecrolimus are related to the activation of T lymphocytes. The typical interaction of the antigen with the T-lymphocyte receptor determines an increase of calcium in the cytosol that forms complex with the calcium-binding protein, calmodulin, which then activates calcineurin. When calcineurin is activated it catalyzes the dephosphorylation of a number of substrates, including N phosphorylated NF-AT (NF-AT) that are supposed to go to the nucleus to regulate the genes transcription.

TABLE 63-1—Topical Pimecrolimus and Tacrolimus: Comparison Between the Two Drugs in Terms of Mechanism of Action and Pharmacokinetics¹⁴

	Pimecrolimus	Tacrolimus
Principal Cellular targets	T cells, mast cells	T cells, mast cells
Cytokines inhibited	IL-2, IL-3, IL-4, IL-5, IFN- γ , TNF- α	IL-2, IL-3, IL-4, IL-5, IFN- γ , TNF- α
Blockade of dendritic cell functions	+	-
Apoptosis of dendritic cells	+	-
Skin penetration	+	++

Tacrolimus can prevent this signaling through the production of a complex with macrophilin-12 and calcium-calmodulin. This complex inhibits calcineurin activity, thereby preventing the dephosphorylation of NF-AT and inhibiting its ability to regulate the transcription of genes.

Tacrolimus can suppress the transcription of a number of genes, that produce interleukin-2 (IL-2), interleukin-3 (IL-3), interleukin-4 (IL-4), interleukin-5 (IL-5), interleukin-12 (IL-12), interferon-gamma (IFN- γ), tumor necrosis factor-alpha (TNF-a), and granulocyte-macrophage colony-stimulating factor (GMCSF), which are relevant in the pathophysiology of several skin disease including atopic dermatitis, vitiligo and psoriasis⁶. As far as pharmacokinetics is concerned, during the clinical development program, systemic exposure to topically applied pimecrolimus and tacrolimus was investigated in short-term and long-term studies to assess systemic percutaneous absorption of topically applied drugs.

The results of these studies⁷ demonstrate that treatment with pimecrolimus cream 1% results in minimal systemic exposure to pimecrolimus during treatment for up to 1 year. The highest pimecrolimus blood concentrations measured in adults was 4.6 ng/mL, while in pediatric patients was 2.6 ng/mL. These levels were lower than the mean peak concentration found in adult psoriatic patients treated for 28 days with a well-tolerated oral dose of 30 mg pimecrolimus twice daily.

Tacrolimus is largely metabolized in the liver by the cytochrome P450 enzyme system via monodemethylation and/or hydroxylation. The drug is then excreted through the bile, which displays most of its metabolites. Less than 1% of the drug is excreted unchanged in the urine.

Sirolimus, like tacrolimus, and pimecrolimus, is a potent inhibitor of T-cell activation, but its mechanism of action is different. Sirolimus inhibits the IL-2 receptor-mediated signal transduction pathway with no effect on calcineurin activity. Instead, the FKBP12/sirolimus complex binds to and inhibits the kinase activity of mTOR, a central kinase that transduces signals from the IL-2 receptor and other growth factor receptors to cell cycle regulators, including p70S6 kinase. TOR proteins play a crucial role in coordinating the equilibrium between protein synthesis and breakdown in response to nutrient availability. Essentially, TOR proteins act on downstream proteins responsible for controlling translation of mRNAs encoding proteins that regulate the cell cycle⁸. These include translation inhibitors, eukaryotic translation initiators (eIF4GI) and ribosomal S6 kinases (S6Ks). A noncytotoxic dose of sirolimus inhibits primary and metastatic tumor growth by interfering with angiogenesis. It induces a decrease in the production of vascular endothelial growth factor (VEGF) and blocks stimulation of vascular endothelial cells by VEGF. This may also be relevant to its mechanism of action in psoriasis, as angiogenic factors are important to the development of disease. Therefore, it can be expected that sirolimus will have a different safety profile, without nephrotoxicity,

neurotoxicity, or hypertension. Preclinical in vitro and in vivo studies have demonstrated that combination treatments of topical sirolimus and oral cyclosporin can result in a synergistic effect and the reason for this is because the two drugs are active in different steps of the cell-mediated immune response.

ANIMAL MODELS: EFFECTIVE AND SAFETY

Sirolimus, pimecrolimus and tacrolimus have been tested in numerous animal studies designed expressly to further explore the toxicity of the molecule and increase drug exposure to observe toxic effects.

Animal models have also been studied in order to evaluate the effectiveness of topical pimecrolimus and tacrolimus. Meingassner et al.^{9,10} made several investigations of allergic contact dermatitis in mouse, rat, and pig models in which topical calcineurin inhibitors showed a very high level of activity. In pig models, a statistically significant anti-inflammatory effect was observed at concentrations as low as 0.04%. Pimecrolimus had no effect on skin texture or thickness and showed an overall effectiveness close to that of potent corticosteroids for the treatment of autoimmune skin disease¹¹.

Neckermann et al.¹² studied the effectiveness of systemic and topical pimecrolimus on hypomagnesemic hairless rats compared to its vehicle. The use of topical pimecrolimus was effective with suppression of the inflammation in five rats treated but at the concentration used in this study, it did not appear to have a systemic effect.

In dermal carcinogenicity studies related to lymphomas performed on mice, systemic immunosuppression was only observed in the mice treated with a high systemic exposure to pimecrolimus.¹³ No evidence of lymphoma was observed until systemic exposure to the drug was 66 times the average systemic exposure measured at the maximum recommended dose of topical pimecrolimus in humans. Concerning tacrolimus, no evidence of lymphoma was observed in analogous murine toxicology studies until systemic exposure to the drug was 26 times the average systemic exposure at the maximum recommended dose of topical tacrolimus estimated from human studies.

In animal models and in humans sirolimus has shown a relevant immunosuppressive activity in a number of diseases. In a murine model of tetradecanoylphorbol acetate-induced ear edema, sirolimus inhibited the edematous response in a dose-dependent manner. In addition, neutrophil infiltration and epidermal influx were significantly inhibited in this model. Sirolimus has been demonstrated to reduce keratinocyte proliferation in a dose-dependent manner. As the proliferative state of keratinocytes and neutrophil infiltration of the epidermis are characteristics of psoriasis, these studies suggest that sirolimus might have a role in the treatment of psoriasis. Topical application of 1.2% sirolimus in a pigskin model of allergic contact dermatitis was ineffective.

TABLE 63-2—Efficacy of Topical Pimecrolimus and Tacrolimus in Inflammatory Skin Diseases

	Pimecrolimus	Tacrolimus	Sirolimus
Atopic Dermatitis	Established efficacy	Established efficacy	-
Vitiligo	Likely beneficial	Likely beneficial	-
Psoriasis	Established efficacy (intertriginous psoriasis)	Established efficacy (intertriginous psoriasis)	Likely beneficial
Seborrheic Dermatitis	Likely beneficial	Likely beneficial	-
Lupus Erythematosus	Likely beneficial	Likely beneficial	-
Alopecia Areata	Possibly beneficial	Possibly beneficial	-
Oral Lichen Planus	Likely beneficial	Likely beneficial	-
Pyoderma gangrenosum	Possibly beneficial	Possibly beneficial	-
Chronic Hand Dermatitis	Possibly beneficial	Possibly beneficial	-
Chronic actinic dermatitis	Possibly beneficial	Possibly beneficial	-
Ichthyosis linearis circumflexa	Possibly beneficial	Possibly beneficial	-

Established efficacy: High-quality meta-analyses, systematic reviews of randomized-controlled trials with a very low risk of bias.

Likely beneficial: Case-control or cohort studies with a high risk of confounding.

Possibly beneficial: Nonanalytic studies.

Topical application of up to 2% sirolimus ointment was ineffective also in a guinea-pig contact dermatitis model, although suppression of keratinocyte proliferation was observed⁹

EFFICACY

Efficacy of tacrolimus, pimecrolimus, and sirolimus has been evaluated in atopic dermatitis, vitiligo, psoriasis, and other skin disease including seborrheic dermatitis, lupus erythematosus, alopecia areata, and others (Table 63-2).

ATOPIC DERMATITIS

Atopic dermatitis (AD) is the most common inflammatory skin disease in children, affecting more than 15% of children in the United States.

Several clinical trials showed efficacy and safety of pimecrolimus in treatment of AD^{14–16}. AD improved after a few days of twice-daily topical application of pimecrolimus and multiple clinical trials have demonstrated an improvement of the eczema area severity index (EASI). The treated patients also showed a significant decrease in the number and severity of flares and a lower dependence on corticosteroids in infants as young as 3 months with atopic dermatitis.

In two independent 6-week randomized-controlled trials, treatment with pimecrolimus 1% cream twice daily significantly decreased the symptoms of AD in children, as well as adolescents as compared to its emollient vehicle. At week 6, 35% of pimecrolimus-treated patients were classified as clear or almost clear of disease according to the investigator global assessment (IGA). The drug showed

a rapid onset of action, with therapeutic effects observed by day 8 and further improvement thereafter¹⁷. The baseline disease severity had no effect on treatment outcome¹⁸. Hanifin et al.¹⁹ reported an improvement of the diseases in children and adults affected by AD treated with topical tacrolimus. A marked reduction in pruritus was seen within 3 days of therapy. Hanifin et al. concluded that tacrolimus ointment therapy is a rapidly effective and safe treatment for the management of atopic dermatitis in both pediatric and adult patients who were followed for up to 4 years.

A randomized-controlled trial compared pimecrolimus cream 1% with tacrolimus ointment 0.03% in pediatric patients with moderate to severe AD. 170 patients (2–17 years) were enrolled into two groups (pimecrolimus vs. tacrolimus). The therapies were applied twice daily until complete clearance of disease or until week 6. As far as efficacy was concerned, there were no statistically significant differences in terms of efficacy between the treatment groups in the proportion of patients achieving clinical success. However, IgA response rates resulted slightly higher in the tacrolimus group²⁰.

VITILIGO

Different treatment options for vitiligo are available. Calcineurin inhibitors seem to represent a useful alternative for vitiligo in particular for locations on the head and neck. The use of Pimecrolimus allows the dermatologist also to avoid the side effects of currently available therapeutic options such as topical steroids. Calcineurin inhibitors can be used alone or in combination treatment.

The additional use of UVB-narrow band phototherapy increases the efficacy of calcineurin inhibitors according

to our experience,²¹ but its long-term safety is no yet clear, in particular regarding the photo-carcinogenic effect. Ostovari et al.²² however, observed that there is a lack of efficacy of tacrolimus in the absence of UV-B exposure.

Grimes et al.²³ for the first time described the efficacy of tacrolimus in vitiligo while Lan et al.²⁴ reported that tacrolimus promotes melanocyte and melanoblast growth and creates a favorable milieu for cell migration via keratinocytes. Kanwar et al.²⁵ reported more than 75% repigmentation in 57.9% and 50% to 75% repigmentation in 26.3% of children treated with topical tacrolimus (0.3%) in vitiligo.

In a double-blind half-side trial comparing topical tacrolimus to clobetasol in 20 children with vitiligo, Lepe et al.²⁶ reported that the two agents were equally effective.

Long-term stability of repigmentation and efficacy of combination therapies among calcineurin inhibitors and other topical agents in vitiligo, however, remain to be further investigated.

PSORIASIS

Topical treatment of psoriasis is usually restricted to the mild form of the disease because the thick scaling seems to inhibit the drug's penetration into the skin. The use of calcineurin inhibitors in psoriasis treatments originated from the observation of seven psoriatic patients that were undergoing organ transplant and had been treated with systemic tacrolimus therapy. This treatment resulted in a dramatic improvement of psoriasis with complete remission in 4 weeks.

Several reports showed the efficacy of calcineurin inhibitors in plaque-type psoriasis.^{27–30} Recently, a task force of the National Psoriasis Foundation Medical Board was convened to evaluate treatment options for this disease³¹. This study group recommended low- to mid-potency topical steroids as first-line, short-term treatment. Calcipotriene (calcipotriol), pimecrolimus, and tacrolimus, for long-term therapy when it is possible.

Zonneveld et al.³² reported that topical tacrolimus instead is ineffective in chronic plaque psoriasis because of poor absorption.

A study³³ conducted using topical sirolimus on 24 patients for 6 weeks showed that topically applied sirolimus penetrates the skin and may have some antipsoriatic and immunosuppressive activity.

SEBORRHEIC DERMATITIS

Seborrheic dermatitis (SD) is a chronic inflammatory disorder that mainly affects the seborrheic region. SD is a chronic relapsing skin disorder that presents with erythema, scaling, and pruritus.

While ketoconazole is often used, pimecrolimus has been used successfully in SD³⁴. The efficacy of pimecrolimus in the treatment of seborrheic dermatitis has been

compared with a potent corticosteroid in an open-label clinical trials and randomized trials.^{35–37} The efficacy of the two different treatments in reducing symptoms of the disease was approximately comparable, but relapses were observed more frequently and were more severe in the corticosteroid group than in the pimecrolimus. Moreover, Koc and colleagues showed that pimecrolimus had also a comparable efficacy profile to that of ketoconazole, but side effects appeared more frequently in the pimecrolimus group than in the ketoconazole group³⁴.

LICHEN PLANUS

Oral lichen planus (OLP) is considered an autoimmune disease of unknown etiology that affects the mucosae, especially the oral cavity. Existing clinical trials have shown that topical corticosteroids are often effective in the management of oral lichen planus. However, tacrolimus has recently been shown to be an effective treatment of OLP. Vente et al.³⁸ treated six patients with erosive oral lichen planus with 0.1% hydrophilic tacrolimus ointment and all reported rapid relief of pain and burning. Radfar et al. compared the effectiveness of clobetasol and tacrolimus in the topical management of OLP,³⁹ and they found tacrolimus to be as useful as clobetasol in the treatment of OLP.

A number of other studies demonstrated the utility of tacrolimus 0.1% and pimecrolimus for the treatment of OLP.^{40–47} Moreover, Donovan et al.⁴⁸ successfully treated the refractory oral lichen planus associated with hepatitis C with tacrolimus.

A recent group case report⁴⁹ conducted in seven patients affected by erosive oral lichen planus, showed good activity of sirolimus in the treatment of this disease with negligible absorption and side effects.

OTHER SKIN DISEASES

There is a long list of small series and case reports documenting the use of pimecrolimus and tacrolimus in various inflammatory skin conditions that warrant further validation.

A few number of clinical trials^{50,51} have shown the potential efficacy of pimecrolimus and tacrolimus in lupus erythematosus where, however, the gold standard of topical treatment remains the high-potency corticosteroid. In our experience, calcineurin inhibitors represent an excellent alternative for treatment of lupus erythematosus where local corticosteroids are contraindicated.

Thiers⁵² tried topical tacrolimus 0.3% in a boy with alopecia areata who subsequently progressed to alopecia totalis. We suppose that the failure of the treatment (in two single cases) relates to an insufficient penetration of the ointment formulation in skin. Since then, however, several animal studies^{53,54} have been performed regarding this concept without consistent result.

Tacrolimus has been suggested for the ulcers of pyoderma gangrenosum.⁵⁵ Reich et al.⁵⁶ successfully treated such lesions with 0.1% tacrolimus ointment twice daily, obtaining clearance within 3 weeks. Marzano et al.⁵⁷ suggested that topical tacrolimus monotherapy could represent a first-line treatment for PG that fulfills the following criteria: localized disease, idiopathic form, and recent onset with negative microbiologic tests on PG lesions.

In an open label study,⁵⁸ performed in patients affected by chronic hand dermatitis, pimecrolimus induced a complete or almost complete clearance in 30% of patients after 22 days of continuous therapy, including overnight occlusion. The authors found that twice-daily topical treatment with pimecrolimus cream 1% resulted in low pimecrolimus blood levels, was well tolerated as well as safe and effective.

A few case reports,^{59–61} describe successful treatments of chronic actinic dermatitis with topical tacrolimus and pimecrolimus have been reported. One case of ichthyosis linearis circumflexa in a 20-year-old man was treated successfully using topical tacrolimus.^{62,63}

It is our opinion that these studies appear promising but require further validation through randomized and double-blind studies in a large sample size and with a significant follow-up period.

SAFETY PROFILE

During the development program, a number of clinical studies were conducted in patients treated with tacrolimus and pimecrolimus for up to 2 years, with no clinically relevant systemic side effects and no clinically significant treatment-related laboratory abnormalities. In studies,^{64–66} all data show that the risk of consistently systemic exposure after topical application of tacrolimus and pimecrolimus is very low risk and the maximum blood concentration in most patients is below the limit of quantification.

In all these clinical studies, application site reactions such as burning sensations and pruritus was the most frequently reported treatment-related adverse event (Table 63-3). These reactions were always short events of mild or moderate severity, which occurred during the first week of the treatment period and often disappeared by the second or third week of treatment.²⁰ The burning sensation, which

is generally experienced as a feeling of warmth or heat, has been reported by 18–59% of patients in clinical trials. Application-site pruritus and erythema were reported by at least 10% of patients in clinical studies and usually temporary. The burning sensation, pruritus, and erythema occurred more frequently in adults than in children.

In the clinical studies, the incidence of application-site side effects seemed to be related to the severity of disease. Compared to patients with less severe disease, more patients with severe disease or with >75% of their body surface area affected reported these events.^{19,67}

In a study conducted with patients that applied either pimecrolimus cream 1% or tacrolimus ointment 0.03% twice daily to all skin lesions until complete clearance and upon recurrence for 6 weeks. Application site reactions were less common in pimecrolimus-treated patients than in tacrolimus-treated patients. In particular, erythema or irritation of the skin was reported by 8% of patients treated with pimecrolimus cream 1% and by 19% of patients treated with tacrolimus ointment 0.03%.

Two 6-week studies⁶⁸ conducted in children with mild to severe AD did not reveal significant differences in the incidence of application site reactions between patients treated with either tacrolimus ointment 0.1% or tacrolimus ointment 0.03% and those treated with pimecrolimus cream 1%.

Common nonapplication site side effects are seen during treatment with tacrolimus ointment include influenza-like symptoms, headache, allergic reaction, and asthma⁶⁹.

Special concern was raised for the development of the skin viral infections. The cutaneous viral infection may be caused by local immunosuppression induced by calcineurin inhibitors. During the studies, the infectious disease (ID) rates for total skin infections and the infection disease rates for total bacterial, fungal and parasitic skin infections were similar in patients treated with pimecrolimus cream 1%, and in patients who received the vehicle. In children, the ID rate of total viral skin infections was instead significantly increased in patients treated with pimecrolimus cream 1% in comparison with placebo⁷⁰.

Occurrence of recurrent skin tags, rosacealike granulomatous eruptions, rosaceiform dermatitis, mucosal hyperpigmentation, tinea incognita, molluscum contagiosum, in addition, verruca vulgaris have been reported.

TABLE 63-3—Incidence of Common Application-Site Adverse Events in Clinical Trials^{55,61}

	Tacrolimus 0.03% ointment (%)		Tacrolimus 0.1% ointment (%)		Pimecrolimus cream 1%	
	Children	Adults	Children	Adults	Children	Adults
Burning sensation	18-43	45-46	19-34	23-59	13.4	25.9
Pruritus	13-41	20-46	11-32	15-46	-	5.5
Erythema	2-8	2-25	1-8	4-28	3.1	2.1

Risk of Malignancies

There is a theoretic concern that topical immunomodulatory therapy with tacrolimus and pimecrolimus may increase the risk of cancer, even if there is no consistent evidence to suggest an increased risk of cutaneous or visceral cancer.

Systemic use of calcineurin inhibitors in transplant patients is associated with lymphoma and skin cancer,⁷¹ however, this association seems related to the immunosuppressive effect of the systemic level of these drugs apparently determined by the administration of high doses for prolonged periods.

There is no clear evidence to suggest that there is a systemic immunosuppression in patients with AD or other skin disease treated with topical calcineurin inhibitors; some data could instead suggest the opposite. In fact, in a study where infants and young children received pimecrolimus cream 1% intermittently for up to 2 years, the incidence rate of common noncutaneous childhood infections declined over time and throughout the second year of treatment. This is a relevant finding because an increased incidence of systemic infections is considered a reliable indicator of immunocompetence^{72,73}.

Arellano et al.⁷⁴ performed a nested case-control study in the PharMetrics database to evaluate the association between topical immunosuppressants and lymphoma in a cohort of patients with atopic dermatitis, but did not find an increased risk of lymphoma in patients treated with topical calcineurin inhibitors.

A recent and up to date report of the largest cohort study conducted to evaluate the association between calcineurin inhibitors and cancer, did not observe an increase in overall cancer rates among subjects with atopic dermatitis, or eczema who were exposed to either topical tacrolimus or pimecrolimus⁷⁵. However, they found that the use of topical tacrolimus might be associated with an increased risk of T-cell lymphoma.

Currently there is no evidence that suggests a relationship between the development of skin cancer according to the dose of drugs administered or to the duration of the treatment. To date more than 21,000 patients have been treated with topical calcineurin inhibitors in clinical trials and if there is an increased risk of malignancies, the long-term use of those drugs in population should give rise to an increasing number of malignancies⁷⁶.

CONCLUSION

Topical calcineurin inhibitors appear to be an effective and safe treatment option for the treatment of AD and may work well in several other inflammatory skin diseases such as psoriasis and seborrheic dermatitides, in particularly when lesions are localized on the face or skin folds. They should be used as an alternative topical agent in instances of failure of conventional therapy. It is our opinion that the

What We Know

- Topical calcineurin inhibitors has broadened the range of drugs available to dermatologic disease
- The most common used ones are tacrolimus and pimecrolimus
- They are both immunomodulators that complex macrocyclic compounds that bind to the intracellular protein macrophilin-12.
- This complex inhibits activity of calcineurin, thereby preventing the dephosphorylation of NF-AT and inhibiting its ability to regulate transcription of genes.
- The therapeutic effects of tacrolimus and pimecrolimus are related to the activation of T lymphocytes.
- Efficacy of calcineurin inhibitors has been evaluated in atopic dermatitis, vitiligo, psoriasis, seborrheic dermatitis, lupus erythematosus, alopecia areata, and others.
- Several clinical trials showed efficacy and safety of pimecrolimus and tacrolimus in treatment of AD.
- Calcineurin inhibitors seem to represent a useful alternative for vitiligo in particular for location in the head and neck.
- In clinical studies for up to 2 years, there were no clinically relevant systemic side effects and no clinically significant treatment-related laboratory abnormalities.
- There is a theoretic concern that topical immunomodulatory therapy with tacrolimus and pimecrolimus may increase the risk of cancer.
- There is no evidence to suggest an increased risk of cutaneous or visceral cancer associated to topical application of calcineurin inhibitors.

studies conducted on calcineurin inhibitors, appear to be promising but require further validation with randomized and double-blind studies in a large sample size, and with a significant follow-up period

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INTRODUCTION

Hypnosis consists of intentional trance induction, deepening, work, maintenance, and termination. Medical hypnotherapy can reduce suffering, promote healing, or help the person alter a destructive behavior pattern. The natural trance state has been used since ancient times to assist in healing.

Each of us experiences the absorption that occurs with mild spontaneous trances daily while watching television or a movie, reading a book or a magazine, or playing a computer game. After appropriate training, a person may intensify this trance state in himself or herself or in another individual, and use this heightened focus to promote mind-body interactions that help to lessen suffering or to enhance healing. The trance state may be induced by using deep slow breathing, relaxation, guided imagery, meditation techniques, self-hypnosis, or hypnosis induction techniques. While people vary in their ability to enter the trance state, most can obtain some benefit from hypnosis.

Reaching agreement on a precise definition of hypnosis has been challenging. Marmer¹ described hypnosis as a psychophysiologic tetrad of altered consciousness, consisting of narrowed awareness, restricted and focused attentiveness, selective wakefulness, and heightened suggestibility. For a more extensive discussion of the definitions and theories regarding hypnosis, see the texts by Crasilneck and Hall² or Barabasz and Watkins.³ Myths abound about hypnosis that tend to overrate, underrate, or distort the true capabilities and nature of hypnosis.

With respect to dermatology, hypnosis may help decrease pain and pruritus in the skin; intervene in psychosomatic aspects of skin diseases; and lead to the resolution of some skin diseases, including verruca vulgaris. In some cases, suggestion without formal trance induction may be sufficient. Sulzberger and Wolf⁴ reported on the successful use of suggestion to treat verrucae vulgaris.

MECHANISMS OF ACTION

While clearly defining hypnosis has been somewhat elusive, there are demonstrable observable changes in functional magnetic resonance imaging (fMRI),⁵ positron emission (PET),⁶ and electroencephalogram (EEG)⁷ in the trance state compared with the normal alert state. One way that

hypnosis may make suggestions more effective is by inhibiting competing negative or distracting thoughts, so that the focus can be solely on the suggestion.⁸ This reciprocal inhibition of thoughts competing with the suggestion can enhance positive reconditioning, by reducing the resistance to change and increasing the focus of attention, while pairing a more desirable conditioned stimulus and response to an unconditioned stimulus. When that unconditioned stimulus is then encountered in real every day life, the new subconscious conditioning (learning) can inhibit old undesirable dysfunctional conditioning (learning), resulting in pattern interrupt and changed responses to the stimulus.⁸

Hypnosis can allow conscious regulation of blood flow and other autonomic functions that are not usually under conscious control. The relaxation response occurring with hypnosis affects the neurohormonal systems that regulate many body functions. Hypnotized volunteers in studies have been able to significantly decrease immediate sensitivity flare reaction of the histamine prick test. The effect of hypnotic suggestion on delayed cellular immune responses was shown to have significant effect on the size of erythema and on palpable induration in one study but no significant effect in other studies⁹.

Braun¹⁰ reported that different allergic responses, dermatologic reactions, and effects on seizure disorders, pain control, and healing occurred in the same individual who had multiple personality disorder (now called dissociative identity disorder), depending on the specific personality present at the moment, demonstrating how much influence the mind can have on physiologic reactions and disease processes. The report also described differences in physiologic responses and disease conditions for selected individuals in hypnotic trance compared to their normal waking state.

Hypnosis may be used to promote healthy behaviors, to decrease situational stress, to reduce needle phobias, to control harmful habits such as scratching, to provide immediate and long-term analgesia, to reduce symptoms such as itching related to diseases, to speed recovery from surgery, and to enhance the mind-body connection to accelerate healing. Skin diseases that have a psychosomatic aspect often respond especially well to hypnosis. Griesemer,¹¹ who was both a dermatologist and a psychiatrist, during 1 year in his practice, recorded the occurrences of emotional triggering of dermatoses in his patients. As a result he developed an emotional triggering index for

various skin diseases, with 100 indicating an every single time emotional influence and zero, indicating no emotional influence on the skin disease.

The responsiveness of skin diseases to hypnosis are also noted in the somewhat outdated book by Scott¹² and in the chapter on the use of hypnosis in dermatologic problems in the text by Crasilneck and Hall.² Koblenzer¹³ also mentions some uses of hypnosis for common dermatologic problems. Grossbart and Sherman¹⁴ discuss mind-body interactions in skin diseases and include hypnosis as recommended therapy for a number of skin conditions in an excellent resource book for patients.

MODES OF MEDICAL HYPNOTHERAPY

Hypnosis is a tool, not a therapy in and of itself. It can be used to help locate and correct psychologic and behavioral roadblocks to healing. Processes that can be enhanced by hypnosis include supportive ego-strengthening therapy, direct suggestion, symptom substitution, psychosomatic hypnoanalysis, and posthypnotic suggestion⁹.

Induction of the hypnotic state in adults is achieved by methods that focus attention, soothe, and/or produce monotony or confusion. The hypnotic state can be induced in children by having the child make-believe that he or she is watching television, a movie, a play, a computer game, or by using some other distractive process that uses the imagination.

Deepening the hypnotic state is achieved by methods that continue to focus attention and soothe and/or produce monotony or confusion. Examples include descending stairs with a numerical count, watching a whirling wheel, floating, and going to a safe place and enjoying the sights, sounds, pleasant odors, and tactile feelings.

Trance maintenance can be obtained by methods that continue to soothe and focus attention. The patient usually maintains some awareness and is able to speak to answer questions without coming out of trance.

Trance work can include simply relaxing and being where the patient would rather be during a dermatologic procedure, or supportive ego strengthening, direct suggestions, symptom substitution, psychosomatic hypnoanalysis, and posthypnotic suggestions.

Relaxation and being where the patient would rather be during a dermatologic procedure is useful for reducing anxiety and reducing any pain associated with the procedure. It includes suggestions to the patient to go in their mind where they would rather be such as at a beach, in a forest, taking a trip, enjoying a hobby, floating, or doing some other enjoyable activity.

Supportive ego-strengthening therapy while in a hypnotic state includes positive suggestions of self-worth and effectiveness. The strengthened ego is better able to repress or confront discordant elements that inhibit healing.

Direct suggestion during hypnosis is frequently used to decrease discomfort from pain, pruritus, burning sensations,

and anxiety. Direct suggestion may produce sufficiently deep anesthesia in highly hypnotizable patients to permit cutaneous surgery with no other anesthetic. Direct suggestion can also be used to reduce repetitive behaviors of skin scratching or picking, nail biting or manipulating, and hair pulling or twisting. Undesirable psychophysiological events such as hyperhidrosis, blushing, and some types of urticaria can sometimes be controlled through direct suggestion. Some skin lesions such as verrucae can even be induced to resolve by using direct suggestion.

Suggestions may be made for symptom substitution. Symptom substitution reconditions the subconscious mediated by hypnosis to replace a negative habit pattern with a more constructive one. For example, scratching can be replaced by another physical activity, such as stiffening the elbows and making a fist until the urge to scratch passes. Stress relievers can be substituted for scratching including athletic activities, artwork, verbal expression of feelings, journaling of feelings, or meditation.

Psychosomatic hypnoanalysis may help patients deal with chronic psychosomatic dermatoses that are nonresponsive to other simpler approaches. LeCron's^{15,16} list of the seven most common factors causing emotional difficulties and illnesses, namely conflicts, motivation, the effect of suggestion, organ language, identification, self-punishment, and the effect of past experiences is a good starting point for exploration in hypnoanalysis. Ewin and Eimer¹⁷ provide a scripted method of detecting and neutralizing the emotional impact of sensitizing or precipitating events. They use ideomotor finger signaling to elicit significant memories that may be preverbal or nonverbal. Results are likely to be much more rapid than with standard psychoanalysis. Only well-qualified and appropriately licensed practitioners should perform hypnoanalysis.

The author reported on the successful use of psychosomatic hypnoanalysis in dermatology¹⁸. The author slightly modified Ewin's mnemonic for LeCron's 7 key factors to the mnemonic COMPASS, as follows: Conflict, Organ language, Motivation, Past experiences, Active identification, Self-punishment, and Suggestion. There is a diagnostic value of screening for psychosomatic factors related to skin disorder triggering or exacerbation using psychosomatic hypnoanalysis. If the focused history and ideomotor questioning for all seven COMPASS factors is negative, it is unlikely that there is a significant psychosomatic component. With one or two COMPASS factors positive, appropriate reframing suggestions may be sufficient, but with more factors positive, more intensive psychotherapy would be appropriate.

Posthypnotic suggestion is often included toward the end of the session, and further strengthening of the effects can be obtained by recording an MP3 or CD that the patient can repeatedly use for self-hypnosis later. The patient should not use the recording while operating a motor vehicle. It often takes 20 to 40 repetitions before a behavioral or attitudinal change is likely to be permanent.

Trance termination may be obtained by suggesting a realerting, with, or without count up, and usually incorporating suggestions for continued relaxation and ease for the rest of the day while becoming fully alert and awake. With self-hypnosis, patients will come out of trance spontaneously either to the alert state or by falling asleep, depending upon the circumstances and the patient's desires.

SEARCH METHODS

A search was conducted using Ovid EBM Reviews - Cochrane Database of Systematic Reviews searching for hypnosis and Ovid MEDLINE 1950 to December 2009 searching for hypnosis and the various skin disorders below with extension of the search by tracing article references back to the 1920s for treatment. Of particular interest were randomized controlled trials (RCT) and nonrandomized controlled trials (NRCT), with case series (CS) and case reports (CR) also included for completeness.

EVIDENCE FOR TREATMENT EFFECTIVENESS

The studies reporting effectiveness of various hypnotherapy treatments were rated in terms of the strength of the scientific evidence according to the American College of Cardiology and American Heart Association (ACC/AHA) guidelines grading schema¹⁹. This involves 3 classes of recommendation 1, 2 and 3, and 3 strengths of evidence A, B, C. Recommendation class 1 is for treatments for which there is evidence or general agreement that the treatment is effective. Class 2 is for treatments where there is a divergence of evidence or opinion about the effectiveness of treatment. Class 3 is for treatments where there is evidence or general agreement that the treatment is not effective. Evidence strength level A is strong evidence based on the results of multiple randomized trials or meta-analyses of such trials. Level B is moderate evidence based on evidence from a single randomized trial or from nonrandomized studies. Level C is weak evidence based on expert opinion, case studies, or standards of care.

EFFICACY OF HYPNOTIC RELAXATION DURING DERMATOLOGIC PROCEDURES AND SURGERY

Many dermatologic procedures can produce pain or anxiety in patients. Skin procedures that may be somewhat painful but usually do not require a local anesthetic include moderate depth chemical peels, cryodestruction of skin lesions, curettage of molluscum, excision of skin tags, extrusion of comedones, incision and expression of milia, laser treatment of vascular lesions, strong microdermabrasion, and sclerotherapy. Dermatologic procedures that usually require a local anesthetic include electrodesiccation

and curettage, incision and drainage of an abscess, laser ablation of skin lesions, liposuction, punch biopsy, shave biopsy, surgical excision, and surgical repair. Cutaneous procedures that may require conscious sedation include deep chemical peels, dermabrasion, laser resurfacing, and extensive liposuction. Adding hypnotic relaxation and/or hypnotic analgesia may benefit the patient during all of these procedures.

Recent experimental evidence has helped to localize the active sites of the mechanisms of pain relief during hypnosis. Faymonville et al. found that pain reduction mediated by hypnosis was localized to the activated mid-anterior cingulate cortex, as observed by using subtraction positron emission tomography (PET).⁶

Freeman et al.⁷ observed significantly greater high theta (5.5-7.5 Hz) activity at parietal and occipital sites, during both hypnosis and waking relaxation in persons who were highly hypnotizable (based on the Stanford Hypnotic Susceptibility Scale, Form C or SHSS:C scores). This was carried out in an electroencephalographic (EEG) study of hypnosis effects versus distraction effects on cold pressor pain, compared with persons who were less hypnotizable. Freeman et al. also found that in persons who were highly hypnotizable, hypnosis provided significantly greater pain relief than distraction or waking relaxation. These individuals also had significantly greater pain relief via hypnosis than those who were less hypnotizable. These PET and EEG studies support state-based theories rather than sociocognitive theories of hypnosis.

Montgomery et al.²⁰ in a meta-analysis of hypnotically induced analgesia found that hypnosis relieved pain in patients with headache, burn injury, heart disease, cancer, dental problems, eczema, and chronic back problems. Their study also quantified the magnitude of hypnoanalgesic effects. For most patients, hypnotic suggestion relieved pain regardless of its type. While light and medium trance states are sufficient for most purposes, a deep trance state is required for hypnotic anesthesia for surgery.

Faymonville et al.²¹ randomly assigned 60 patients undergoing plastic surgery with adjunctive conscious sedation either to a control group with stress-reducing strategies or to a hypnosis group. In the hypnosis group, the intraoperative and postoperative anxiety and pain were significantly lower and significantly smaller amounts of medication were required for conscious sedation.

Mauer et al.²² evaluated 60 patients who underwent hand surgery and received either standard treatment or standard treatment with adjunctive hypnosis. The hypnosis group had significantly decreased perceived pain intensity, expression of perceived pain, and anxiety compared to those of control subjects. Patients in the hypnosis group also had significantly fewer medical complications and a more rapid postoperative recovery rate.

Montgomery et al.²³ studied 20 women having excisional breast biopsies who were randomized to standard care versus preoperative hypnosis. They found brief

10 minute hypnosis to be effective in reducing postsurgery pain and distress both before surgery and after surgery.

Defechereux et al.²⁴ reported a prospective randomized study of thyroid and parathyroid procedures performed using hypnosis, local anesthesia, and minimal conscious sedation compared to similar surgery performed under conventional anesthesia. They found that patients in the hypnoanesthesia group had significantly less inflammatory response, hemodynamic dysregulation, postoperative pain, postoperative fatigue, and convalescence time compared with the control group. Bleeding, operative times, and surgical comfort were similar in both groups.

Liossi et al. conducted a prospective, randomized, controlled trial to compare the efficacy of a local anesthetic (EMLA), EMLA plus hypnosis, or EMLA plus attention in children receiving venipuncture. Children in the EMLA-plus-hypnosis group reported less anticipatory anxiety and less procedure-related pain and anxiety. They were rated as demonstrating less behavioral distress during the procedure than patients in the other two groups. In addition, parents whose children were randomized to the EMLA-plus-hypnosis group experienced less anxiety during their child's procedure than parents whose children had been randomized to the other two groups²⁵.

Lang et al.²⁶ conducted a large prospective randomized trial of adjunctive nonpharmacologic analgesia for invasive percutaneous vascular radiologic procedures in three groups: (1) standard intravenous conscious sedation care, (2) structured attention with conscious sedation, and (3) guided self-hypnotic relaxation with conscious sedation if needed. Pain scores increased linearly with time in the standard group and in the structured attention group, but remained flat in the hypnosis group. Anxiety scores decreased over time in all three groups but more so in the hypnosis group. Conscious sedation drug use was significantly higher in the standard group, intermediate in the structured attention group, and lowest in the self-hypnosis group. Hemodynamic stability was significantly higher in the hypnosis group than in the other two groups. Length of procedure times were significantly shorter in the hypnosis group than in the standard group. Individual imagery was quite varied from one patient to another²⁷.

Lang et al.²⁶ concluded that hypnosis was superior in reducing pain and anxiety, in maintaining hemodynamic stability, and in shortening the procedure time compared with standard care, and the results of the structured attention group were in between those of the hypnosis group and the standard care group. Multiple RCT evidence has demonstrated that hypnosis for procedural pain and anxiety is definitely beneficial in invasive radiology as well as plastic surgery, hand surgery, neck surgery, and breast biopsy in adults, and venipuncture in children, evidence class 1A.

Lang and Rosen,²⁸ performed a cost analysis of standard intravenous conscious sedation compared to intravenous conscious sedation that included self-hypnotic

relaxation using the data from the above study. The average cost per case associated with standard care sedation was \$638 compared to an average cost of \$300 per case for hypnosis augmented sedation. The cost savings averaged \$338 per case.

Allowing the patient to choose his or her own self-guided imagery seems to permit most individuals to reach a state of relaxation during procedures. The author has used a technique similar to the invasive radiologic studies modified for dermatology with good success in dermatologic surgery.²⁹ The eye-roll induction is most commonly used by the author, and this method works quickly for most patients. The author is currently conducting a RTC in hypnotic relaxation for dermatologic surgery. Hypnosis for procedural pain and anxiety is probably beneficial in dermatology procedures, with evidence class 1C.

EFFICACY OF HYPNOTHERAPY FOR SPECIFIC DERMATOLOGIC CONDITIONS

Information about the effectiveness of hypnosis on specific dermatologic conditions has in the past largely been based on one or a few uncontrolled cases. In recent years, a few RCT have produced more reliable information. Unfortunately, RCT results are still not available for most of the disease categories. The list of dermatologic conditions below for which hypnosis has been utilized is not all-inclusive, but it does include most of the dermatologic conditions for which hypnosis has been shown to be reasonably helpful in reducing symptoms or in improving aspects of the condition. They are arranged in order based on the strength of scientific evidence for the effectiveness of hypnosis, starting with the strongest RCT evidence, followed by NRCT, CS, and CR⁹. Dermatologic conditions supported by only one or a few case reports are listed in alphabetical order toward the end of this section, starting with acne excoriée. References not included here can be found in reference 9.

Randomized-Controlled trials

Verruca Vulgaris

The report by Sulzberger and Wolf⁴ on the efficacy of suggestion in treating warts has since been confirmed numerous times. Numerous case series reports attest to the efficacy of hypnosis in treating warts.^{30,31} Ewin reported a case series of warts resistant to other measures including hypnosis where 33 of 41 cleared following psychosomatic hypnoanalysis.³² Several RCT have been performed that demonstrated significant clearing of warts using hypnosis. Spanos et al³³ in a well-conducted randomized-controlled study serves as a typical example, and found that 53% of the experimental group had improvement of their warts 3 months after the first of five hypnotherapy sessions, while

none of the control group had improvement. Hypnosis can be successful as a therapy for warts, evidence class 1A, and hypnoanalysis also can be useful, evidence class 1C.

Psoriasis

Excess stress is often a factor in the onset, exacerbation, and prolongation of psoriasis. Hypnosis and suggestion have been reported to have a positive effect on psoriasis. In a typical case report, 75% clearing of psoriasis was reported by using a hypnotic sensory-imagery technique. Extensive, severe psoriasis of 20 years' duration showed marked improvement in another case by using sensory imagery to replicate the sensations in the patient's skin that he had experienced during sunbathing. Yet another case of severe psoriasis of 20 years' duration fully resolved with a hypnoanalytic technique.

Tausk and Whitmore³⁴ performed a small randomized controlled trial using hypnosis as adjunctive therapy for psoriasis, with significant improvement in individuals who were high hypnotizables as rated by SHSS:C. Hypnosis can be useful as adjunct therapy for resistant psoriasis, especially if an emotional factor is significant in the triggering of the psoriasis, evidence class 1B.

Nonrandomized Controlled Trials

Atopic Dermatitis

Stewart and Thomas³⁵ treated with hypnotherapy 18 adults with extensive atopic dermatitis whose conditions had been resistant to conventional treatment. In a NRCT, they used relaxation, stress management, direct suggestion for nonscratching behavior and for skin comfort and coolness, ego strengthening, posthypnotic suggestions, and instruction in self-hypnosis. The results were statistically significant for reduction in itching, scratching, sleep disturbance, and tension compared with controls. Topical corticosteroids use decreased from the original amount for each patient by 40% at 4 weeks, 50% at 8 weeks, and 60% at 16 weeks, evidence class 1B. For resistant atopic dermatitis, hypnosis can also reduce the required amount of other conventional treatments.³⁶

Case Series

Alopecia Areata

Gupta et al³⁷ noted a strong correlation between high stress reactivity and depression in patients with alopecia areata. Not all reports of hypnosis for alopecia areata have produced positive results. Willemson et al³⁸ utilized hypnotherapy for 21 patients, of whom nine had alopecia universalis and 12 had extensive alopecia areata. All patients had significantly lower anxiety and depression after

hypnotherapy. Complete scalp hair regrowth occurred in nine patients, including four with alopecia universalis and 2 with ophiasis. Over 75% scalp hair regrowth occurred in another 3 patients. Five patients had a significant relapse of alopecia, evidence class 2C.

Urticaria

Two individual cases of urticaria responding to hypnotic suggestion were reported in a study. An 11-year-old boy had an urticarial reaction to chocolate that could be blocked by hypnotic suggestion so that hives appeared on only one side of his face in response to that hypnotic suggestion. A case series study of hypnosis with relaxation therapy utilized for 15 patients with chronic urticaria of an average duration of 7.8 years showed that within 14 months, six patients' conditions had cleared and eight had improved, with decreased medication requirements reported by 80% of patients. One patient's condition did not improve, evidence class 2C. Ewin¹⁷ described a case where psychosomatic hypnoanalysis uncovered a history in a medical student who had urticaria to chocolate. As a young boy he had gone to a local zoo with his parents and happened to be looking at the python cage at feeding time. He was horrified to see a python swallow a bunny rabbit. The next morning for Easter he got an Easter basket containing a chocolate bunny. That was when the urticaria to chocolate began. Once the medical student became aware of his own childhood memories and processed them as an adult, along with posthypnotic suggestions that it would be safe for him to eat chocolate without reacting, he could eat chocolate with no reaction.

Individual Case Reports

Acne Excoriée

Hollander³⁹ reported success in controlling the psychogenic picking aspects of acne excoriée in two cases, by using posthypnotic suggestion that the patient was to remember the word scar whenever she wanted to pick her face and to refrain from picking by saying scar. The excoriations resolved but not the underlying acne. The author has also used this technique successfully, along with suggestions that natural with slight imperfections is really more beautiful than something artificially perfect, evidence class 1C.⁴⁰

Congenital Ichthyosiform Erythroderma

Several cases of remarkable clearing of congenital ichthyosiform erythroderma of Brocq following direct suggestion for clearing under hypnosis have been reported. For example, Kidd⁴¹ reported improvement in a 34-year-old father and his 4-year-old son. Not all cases have responded so well, however, evidence class 2C.

Dyshidrotic Dermatitis

A reduction in the severity of dyshidrotic dermatitis has been reported with hypnotherapy treatment. Greisemer's¹¹ data indicate a significant psychosomatic component for dyshidrosis; therefore, hypnosis has biologic plausibility as a therapy. Not all reports have been positive, evidence class 2C.

Erythema Nodosum

Resolution of erythema nodosum of 9-year duration occurred in a 44-year-old woman after hypnoanalysis¹⁸. Five of the seven key COMPASS factors were positive in this case. Because so many factors were positive, the patient was referred for psychotherapy but failed to follow up on the psychotherapy, evidence class 1C.

Erythromelalgia

One case report exists of successful treatment of erythromelalgia in an 18-year-old woman using hypnosis alone followed by self-hypnosis. Permanent resolution occurred. Not all cases respond, evidence class 2C.

Furuncles, Recurrent

Jabush⁴² described a 33-year-old man with recurrent multiple furuncles since age 17 years old that contained *Staphylococcus aureus*. The furuncles were unresponsive to multiple treatment modalities. He noted that the patient had a negative self-image. Use of hypnosis and self-hypnosis with imagined sensations of warmth, cold, tingling, and heaviness resulted in dramatic improvement over 5 weeks, with full resolution of the recurrent furuncles. The patient also improved his self-image substantially. The hypnosis was hypothesized to have helped in some way to normalize the immune response of the body to the bacteria. While conventional antibiotic therapy is the first line of treatment for furuncles, in unusually resistant cases with significant psychosomatic overlay, hypnosis may help to end the recurrent cycles of infection, evidence class 1C for recurrent furuncles with psychosomatic overlay.

Glossodynia

When oral pain has a psychogenic component, hypnosis may be effective. Even with purely organic disease, hypnosis may temporarily relieve pain, evidence class 1C.⁴³

Herpes Simplex

Reduction in the frequency of recurrences of herpes simplex following hypnosis has been reported along with lessening of discomfort from herpes simplex eruptions.⁴⁴

In patients with an apparent emotional trigger factor, hypnotic suggestion may be useful as a therapy for reducing the frequency of recurrence, evidence class 1C for lessening of discomfort.

Hyperhidrosis

Hypnotherapy and autogenic training may be useful as adjunctive therapies for hyperhidrosis but have variable success, evidence class 2C.

Ichthyosis Vulgaris

A 33-year-old man who had ichthyosis vulgaris that tended to be better in the summer and worse in the winter began hypnotic suggestion therapy in the summer and was able to maintain the summer improvement throughout the fall, winter, and spring. Other cases have not had significant improvement, evidence class 2C.

Lichen Planus

The pruritus and the lesions may be reduced in selected cases of lichen planus by using hypnotherapy, but results are mixed, evidence class 2C.

Neurodermatitis

Several cases of neurodermatitis or psychogenic excoriations have reportedly resolved by using hypnotherapy. The neurodermatitis remained resolved, with up to 4 years of follow-up.⁴⁵ Iglesias⁴⁶ reported 3 cases of neurodermatitis that failed to respond to direct suggestion under hypnosis but that responded to hypnoanalysis with ideomotor signaling followed by reframing, evidence class 1C.

Nummular Dermatitis

A reduction of pruritus and resolution of lesions have been reported with the use of hypnotherapy for nummular dermatitis, with mixed results, evidence class 2C.

Postherpetic Neuralgia

In some individuals, the pain of acute herpes zoster and postherpetic neuralgia can be reduced by hypnotherapy, with mixed results, evidence class 2C.

Pruritus

The intensity of pruritus may be modified and improved by hypnosis. For example, a man with chronic myelogenous leukemia had intractable pruritus, which improved with hypnotic suggestion. Hypnotherapy evidence for reducing

pruritus including that in atopic dermatitis is evidence class 1B.

Rosacea

Rosacea, especially the vascular blush component, has been reported to improve in selected cases of hypnotherapy for resistant rosacea, but not in others, evidence class 2B.

Trichotillomania

Several cases of successful adjunctive treatment of trichotillomania with hypnosis have been reported. Hypnotherapy for trichotillomania is evidence class 1C⁴⁷.

Vitiligo

Hautmann and Panconesi⁴⁸ described the psychoneuroendocrinimmunologic aspects and mechanisms of vitiligo. Occasional cases of vitiligo have improved by using hypnotic suggestion, but most do not, evidence class 3C.

SAFETY PROFILE FOR HYPNOSIS

In appropriately selected patients, hypnosis can decrease or eliminate symptoms, and in some cases, it can induce lasting remissions or cures of skin diseases. Discussing this option with patients allows the dermatologist to gauge the patient's receptiveness to hypnotherapy. The time requirements for screening patients, educating them about realistic expectations for results from hypnosis, and performing the hypnotherapy are generally no longer than those for screening, preparing, and educating patients about cutaneous surgery and then performing it.

Many dermatologists choose to refer patients with complex psychosomatic dermatologic problems to competent specialists in hypnotherapy. Dermatologists who prefer to refer patients to hypnotherapists may obtain referrals and information from the American Society of Clinical Hypnosis www.asch.net or similar professional organizations. Dermatologists who prefer to learn how to use hypnosis themselves may obtain appropriate training through the same organizations.

The advantages of medical hypnotherapy for dermatologic diseases include the ability to obtain a response where other treatment modalities have failed, the ability to reduce relapses, and the ability of patients to self-treat and gain a sense of control when taught self-hypnosis reinforced by using audio recordings. Hypnosis is nontoxic and cost-effective. Providing this treatment can result in pleased and grateful patients.

The disadvantages of medical hypnotherapy in dermatology include the training required, the low hypnotizability of some patients, the negative social attitudes still prevalent about hypnosis, and the lower reimbursement

rates per unit time for cognitive therapies such as hypnosis when compared to procedural therapies such as cutaneous surgery. An occasional patient can experience a mild post-hypnotic headache.

TRAINING IN MEDICAL HYPNOTHERAPY

The American Society of Clinical Hypnosis offers weekend, regionally held, 20-hour courses in beginning, intermediate, and advanced hypnosis. Information may be obtained from its web site www.asch.net, which also provides online registration for the courses. Other organizations also offer training both in the United States and abroad. Once the practitioner has obtained the necessary basic training, mentors are available.

LEGAL ASPECTS OF PRACTICING MEDICAL HYPNOTHERAPY

In some states in the United States such as Florida, the practice of hypnotherapy is limited to licensed practitioners. The training requirements depend on the type of license. Outside of the United States, most jurisdictions have their own laws or statutes that dictate who may legally practice hypnosis.

As with all medical practice, informed consent is crucial before proceeding with medical hypnotherapy. Although the informed consent does not need to be in writing, informed consent should be well documented in the patient's chart if no written form is signed by the patient.

In some states, prior hypnosis may be considered to taint the accuracy of the memory with respect to legal testimony given by patients if they are plaintiffs, victims, or witnesses. If the area to be addressed by medical hypnotherapy might be open to future litigation, the credibility of the patient's testimony may suffer. When applicable, this potential legal issue should be included in the informed consent discussion.

Exploring repressed memories is a legally risky issue because of legal claims by patients that hypnotherapists have created false memories. Only adequately trained physicians, psychiatrists, and psychologists who know how to avoid asking leading questions should venture into this area.

This information is not warranted to be legally correct. Conferring with a qualified attorney to obtain legal advice is recommended to obtain correct information for a specific jurisdiction.

PATIENT SELECTION FOR MEDICAL HYPNOTHERAPY

Suitable patients for hypnosis are mentally intact, not psychotic or intoxicated, motivated, not resistant, and preferably moderately or highly hypnotizable, as rated

What We Know

- Hypnosis for procedures has strong supporting evidence, as does hypnosis for warts and for atopic dermatitis. RCT and NRCT for most dermatologic conditions have yet to be performed, with only the weaker evidence of CS and individual CR to support the use of hypnotherapy in those situations. Similarly, psychosomatic hypnoanalysis has only CS and individual CR to support its use in dermatology.

by the Hypnotic Induction Profile⁴⁹ or by the Stanford Hypnotic Susceptibility Scale and its variants. However, for dermatologic procedures, a moderate or high degree of hypnotizability is not critical to the success of self-guided imagery for relaxation and discomfort reduction.

Hypnotherapy for dermatologic disorders generally works best in moderately to highly hypnotizable patients who are appropriately motivated and who have dermatoses that have a large psychosomatic component or are otherwise known to be responsive to intervention with hypnosis. Starting initially with simple, easy cases is best, referring the more complex cases to those with more experience.

CONCLUSION

Hypnotherapy for dermatologic disorders or procedures can be effective, cost-effective, nontoxic, and gratifying in many cases. For some patients it appears to work miracles and for others to fail completely, while most results lie somewhere in between. A key factor in producing positive results is the specific type of hypnotherapy chosen. Careful selection of the cutaneous disease process, the patient, and the provider, as well as appropriate use of hypnosis, can decrease suffering and morbidity from skin disorders with minimal adverse effects.

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Photodynamic Therapy

65

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INTRODUCTION

Topical photodynamic therapy (PDT) use in dermatologic practice is thoroughly discussed and debated in the scientific literature because although the concept is simple, the multiple parameters involved make it complex, and more studies and research are required to determine the optimal parameters for the treatment of approved as well as off-label indications. Various photosensitizing agents and their different uses in delivery and incubation times, such as being combined with various parameters relating to light, are used. The only FDA-approved (Food and Drug Administration) indication of ALA (5-aminolevulinic acid)-PDT and MAL (methyl aminolevulinate)-PDT is the treatment of actinic keratoses (AKs). MAL-PDT is approved for AK, superficial/nodular basal cell carcinoma (s/n BCC) and Bowen's Disease (BD) in 22 European countries, as well as New Zealand and Australia, where it is marketed under the trade name Metvix® (Photocure, Oslo, Norway and Galderma, Paris, France) and has recently been launched under the name Metvixia® in USA. Levulan® (DUSA Pharmaceuticals Inc.) is the other proprietary drug (ALA 20% solution in an alcohol-water-surfactant vehicle) that has been approved but only for actinic keratoses in the United States and Canada (although not in European countries). Different from the US, ALA is not yet in the pharmacopeia of any European country and can be produced and commercialized only as a chemical reagent. Therefore, its use is subject to the rules and specific authorizations of local ethics committees and national health regulatory authorities.

Currently, there is not enough information to decide whether ALA-PDT is more or less effective, safe, or tolerated than MAL-PDT. ALA-PDT has never been evaluated with randomized-controlled studies and this makes comparison of the results obtained from various studies extremely difficult. In addition, even if ALA has been used in many studies as an occlusive medication at a standard concentration (20%) therefore the type and modality of preparation and conservation of the drug, time of application, emission spectrum, and dosage of irradiated light were very different. ALA/MAL PDT has been investigated in the off-label treatment of a number of other neoplastic, infectious, and inflammatory skin conditions with variable and often contrasting results. The use of ALA/MAL-PDT

in these indications must follow all the rules and authorizations specified by the local Ethics Committees.

The literature was screened by using the top sources (Cochrane Library, the Medline and Embase databases, primary, and secondary journals) for finding the best evidence about treatment for the most recent and definitive studies especially for registered indications that are first discussed and followed by a review that covers the type of scientific study, efficacy in human studies, treatment regimen, longevity/recurrence rates and safety profile.

MECHANISM OF ACTION AND PHARMACOKINETICS

Basically, photodynamic action requires the presence and interaction of three components: a photosensitizer, light (at wavelengths that are absorbed by the photosensitizer) and oxygen. Various light wavelengths, exposures, and intensities are then used to activate the agent. This light-activated molecule interacts with oxygen and leads to the formation of a highly reactive singlet oxygen. With low-light and low-drug doses, cell viability may be obtained while other traits (cytokine formation, receptor expression) may be altered. With higher doses of light and drug, the disruption of cell membranes and organelles causes necrosis. At an intermediate combination of light and drug, cells may undergo apoptosis. The most effective wavelength (which allows for a deeper penetration into the skin) in ALA/MAL-PDT was found to be 635 nm red light and its efficacy is proportional to the light energy rate (W/cm^2) and the energy density or fluence (J/cm^2) used.¹ The topical material (with no intrinsic photosensitizing properties) is converted in the mitochondria to light-absorbing PpIX (in the absence of light, PpIX is metabolized fully to a photodynamically inactive heme over 24 to 48 hours) that accumulates in neoplastic cells or in the endothelium of newly formed vessels of tumor parenchyma while sparing the surrounding healthy tissue. This selectivity is based on photosensitizer size and lipophilic/hydrophilic characteristics, electric charge and unspecific protein binding characterizing some pharmacokinetics differences from ALA (polar hydrophilic molecule) and MAL (more lipophilic molecule) (Table 65-1).^{2,3} In addition to MAL and ALA, other photosensitizers such as benzoporphyrins, phthalocyanines, and porphycenes

TABLE 65-1—Pharmacokinetics Differences from ALA and MAL

Pharmacokinetics	
ALA	Polar hydrophilic molecule. Penetrates cells through a transmembrane active mechanism Na^+/Cl^- -dependent β -amino acid, including glycine and gamma aminobutyric acid (GABA) transporters. This system is energy, pH, and temperature dependent. It is saturable and slow and only slightly accelerated in tumor cells.
MAL	Lipophilic methyl ester of 5-ALA. Penetrates cell membranes with active mechanisms but also by passive transmembrane diffusion. This mechanism does not require energy and is faster. The system is unsaturable; it is very efficient in normal cells but even more efficient in neoplastic cells. MAL is quickly demethylated to ALA in the cytoplasm so that the subsequent metabolic passages are the same.

have been used after local application in some pilot studies. Compared to PpIX, these molecules are characterized by a higher absorption coefficient, improved bioavailability and an absorption peak in the range of distant red ($\lambda > 660$ nm) or near infrared ($\lambda = 700-850$ nm) regions that allows them to be activated even as deep as the hypodermis. Their use is still experimental and reserved to selected researcher groups.

A photosensitization mechanism is initiated by the absorption of light by a photosensitizer (P) which generates an excited state of P with two main kinds of competing pathways: a type-1 mechanism where the excited state of the photosensitizer interacts directly with the substrate molecule. The reaction proceeds by electron or hydrogen atom transfer and leads to the formation of reactive oxygen species (ROS: hydrogen peroxide, superoxide radical anion and hydroxyl radical) which oxidize a wide variety of biomolecules causing biologic damage and a type-2 mechanism where the photosensitizer reacts with molecular oxygen to produce a highly reactive oxygen intermediate that easily initiate further reactions. Both type-1 and type-2 reactions cause oxidation of biomolecules in the cell but 1O_2 is regarded as the main mediator of phototoxicity in PDT. The reactive oxygen proceeds to destroy the target cell by direct effects with necrosis but especially apoptosis with lipids, amino acids, and protein oxidation; vascular effects with damage to endothelial cells by platelet activation and release of proaggregatory agents from leucocytes

that leads to ischemia and eventual tumor necrosis and induction of innate and adaptive immune responses, with up-regulation of inflammatory mediators and infiltration of neutrophils, lymphocytes and macrophages that contribute to the damage of tumoral tissue.³

The precise mechanisms (at a cellular level) underlying the efficacy of topical PDT in the treatment of NMSC (nonmelanoma skin cancer) are not fully known. Both apoptosis and necrosis have been described as occurring after topical PDT and the importance of each phenomenon may be influenced by an intracellular localization of the photosensitizer and illumination parameters.^{4,5}

TREATMENT MODALITY AND SAFETY PROFILE

First, it is important to note general exclusion criteria, which were implemented by all reviewed studies. PDT should not be used in patients with any type of photosensitivity, a photosensitizing disease, or even recently tanned skin. Patients with a previous erythema or an inflammation at the treatment site must have had a complete resolution of these conditions prior to treatment or re-treatment.

ALA and MAL are contraindicated for patients with cutaneous sensitivity at 400-450 and around 630 nm, porphyria, allergies to porphyrins or sensitivity to any components of the ALA/MAL solution. Both ALA/MAL are classified as FDA Pregnancy Category C and are not approved for use in children. We summarized (Table 65-2) the most important steps beginning with a preliminary visit to response evaluation as well as safety and management of complications that reflect the most important and recent guidelines. For this reason, the authors suggest finding more details and protocol algorithms from the most important guidelines in order to find also some practical pearls of wisdom.⁶⁻¹⁴ Moreover, you can find in this text, categorized by all relevant cutaneous diseases, the safety profile in addition to the efficacy date.

EFFICACY

Actinic Keratosis

Actinic keratosis (AK) is an important feature of chronic sun damage and helps to identify a population at risk of developing an invasive squamous cell carcinoma (SCC), either from a pre-existing AK or from the surrounding skin. Patients with diffuse signs of photocarcinogenic AKs may experience difficult therapeutic management, especially if those subjects are chronically photoexposed because of professional or lifestyle reasons. In these cases, lesions are usually widespread and tend to recur. It is impossible to predict which AK will evolve into an invasive SCC but it is certain that AK is being recognized increasingly as an early clinical manifestation of a biologic continuum that may ultimately lead to invasive SCC. As it is currently impossible

TABLE 65-2—Multistep Treatment Modality of PDT

STEP 1 <i>Preliminary visit</i>	I. Disclose a personal or familiar history of porphyria or other relevant photosensitivity disorders. II. Documented allergy to the photosensitizer or compounds of the vehicle III. Exclusion criteria IV. In cases of dubious diagnosis, punch biopsy is performed. V. Compilation of the patient's clinical history and the flow chart and measurement of the two diameters of the lesions to be treated. Preoperative photographs are helpful to adequately assess the treatment result and to monitor long-term responses. VI. Evaluate the possible presence of other lesions in other sites, which may require treatment. VII. Inform the patient about the PDT method, possible side effects, and available alternative therapies. VIII. Written consent form.
STEP 2 <i>Preparation of the lesion</i>	I. Scales and crusts may be gently removed, if a keratolytic has not been used, with a curette without local anesthesia. II. In case of bleeding, apply 1% tranexamic acid or 5% acetic acid or 20 vol. hydrogen peroxide or gauze under light pressure until bleeding has stopped. If hemostasis does not occur, postpone treatment to the following day. III. Apply MAL/ALA cream extending the application to 5 mm outside visible margins of the lesion in such a way as to cover the lesion by 1-2 mm. IV. Cover the treated area with polyethylene or adhesive tape, paying particular attention to sensitive areas (around the eyes) and curved zones (around the nose). In these cases, it is advised that the medication be reinforced with a bandage to guarantee the best adherence of the medicine to the skin and to avoid a loss of photosensitization. V. Cover the occlusion to avoid passage of light and the possible deactivation of the PpIX by using gauze and adhesive bandage. VI. The patient can rest for 3 h for MAL while awaiting illumination but should not stay in environments under 15°C. The FDA-approved incubation period for 5-ALA PDT treatment of actinic keratoses is 14-18 hrs, as directed on the package insert for 5-ALA. However, short-incubation times of 1, 2, and 3 hours have been used for treatment of AK. VII. This kind of preparation can be reduced to one step, whereas new patch formulation should highlight relevant clinical results with long-term efficacy. (See AKS paragraph).
STEP 3 <i>treatment</i>	I. The patient should lie down in the most comfortable position possible. II. Remove the bandage (depending on the photosensitizer and the incubation period chosen). III. Both the patient and physician should wear protective glasses. IV. Observation with Wood's light is useful for evaluating the true extension of the lesion to be treated. V. Illumination phase. The three major sources in the USA are the BLU-U (with a delivered dose of 10 J/cm ² for 16 min and 40 s), the pulsed dye laser (PDL) and the intense pulsed light (IPL). A red light (broadband and LED light) is used to a lesser extent in the USA and more commonly in Europe. In this case, the recommended dose is 37 J/cm ² for the LED lamps and 75-100 J/cm ² for filtered halogen lamps. VI. The patient may experience a heating or burning sensation during the first minutes of treatment; in this case, the treatment may be interrupted and restarted a few minutes later. VII. Ask the patient about the intensity of pain (expressed in a VAS—visual-analog scale from 1-10) and report this value on the patient's chart.
STEP 4 <i>After treatment</i>	I. The skin (erythematous or erythemato-edematous, and sometimes exudative) should be medicated with antibiotic cream and covered with gauze. II. The patient should continue this medication for the next few days. III. The patient should be advised not to use steroid creams or cosmetics until the skin is healed. IV. The treated area can be washed daily with water and a delicate detergent. V. The patient may experience a mild burning sensation in the treated area for up to 24 hrs after treatment. If this is intense, the patient may take an oral analgesic. VI. The patient must not expose him/herself to sunlight or UV light until complete re-epithelialization. Serohematic crusts may form in the treated area but should not be removed. VII. It is important to re-evaluate the patient 7 days afterwards and on that occasion, to decide whether further treatment is necessary.
STEP 5 <i>Response evaluation (approved indications)</i>	I. For AKs , a single treatment is sufficient in most cases. Nevertheless, a second treatment may be given, if at follow-up, the lesion has not been removed clinically. If after two sessions the patient has not obtained a complete response, an alternative therapy should be recommended (see AK paragraph for more details). II. All patients with BCC should receive two treatments, 7 days apart. A third treatment can be administered if the lesion is still clinically evident after 1 month of time. Schedule the clinical follow-up at 3 months following treatment and then every 6 months. If the lesion has not completely disappeared after three treatments, the patient should undergo alternative treatment (see BCC paragraph for more details). III. For BD , 1-4 treatments are necessary with the same protocol used for AKs and BCCs (see BD paragraph for more details).

(Continued)

TABLE 65-2—Multistep Treatment Modality of PDT (*Continued*)

STEP 6 <i>Safety and management of complications</i>	<ul style="list-style-type: none"> I. Unlike topical chemotherapy, topical PDT application is not a protracted treatment, with skin contact lasting a few hours to a day, rather than for many weeks or months. Consequently, morbidity and side effects with PDT are diminished relative to those with topical chemotherapies (5-fluorouracil, imiquimod, diclofenac sodium). II. Treatment-associated discomfort is also usually limited, with burning, pruritis, desquamation, crusting, edema, erythema, and pain diminishing within 24 hours of treatment. III. In most cases, symptoms and signs clear entirely within 1-2 weeks. IV. Usually the last manifestations to be resolved are mild erythema and edema limited to the treated region, which is followed by a minimally noticeable, dry necrosis that lasts no more than 3 weeks from the time of treatment. V. Pigment changes, where present, are temporary. VI. Scarring, ulceration, or infection are not reported. On the other hand, consistently satisfactory cosmetic results are regularly noted by investigators. VII. Decreased symptoms may be achieved with concurrent cold air analgesia at the time of initial treatment. VIII. Emollient with a bland moisturizer for several days after treatment and a strict avoidance of light for 48-72 hours after treatment is sufficient to induce rapid resolution of edema and erythema. IX. It is not yet known if PDT can induce malignant transformation. Studies have shown no carcinogenic potential or even delayed onset of neoplasia.
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to determine which lesions will transform, there is a growing recognition of the role of prevention, (e.g., sunscreen), as well as the importance of treating all existing lesions.

Immunosurveillance can modulate the progression of AKs towards neoplastic lesions in single subjects. Grafted or immunocompromised patients usually have widespread AKs with a more rapid progression towards malignancy resulting in areas of field cancerization.^{15,16}

In the treatment of AKs, the new concept of “field cancerization” is very important. This concept was developed in order to explain the growth of multiple primitive tumors and their local recurrence following treatment. Recent studies at a molecular level have supported a cancerogenic model in which the development of a field of genetically modified cells plays a key role. The diagnosis and treatment of epithelial carcinomas, therefore, should not be limited to the single lesion but should also be extended to the field in which it developed, and in which genetic alterations and an initial, gradual replacement of normal cells may already be active. This consideration becomes particularly important when choosing the most appropriate AK treatment, in order to guarantee that the area surrounding the documented lesion may be adequately treated and a therapy such as PDT may be particularly well suited.¹⁷

The aims of this therapy are to eradicate clinically evident and subclinical lesions, as well as the small foci or transformed clonuses, prevent the evolution of an invasive SCC, determine a longer remission, and increase the interval between treatment sessions.

AK was the first FDA-approved indication for the use of PDT in skin cancer management and a large body of evidence now exists to support the use of photodynamic therapy for the treatment of AK (Figures 65-1a and 65-1b).

The treatment of actinic keratosis has been shown to be efficacious in large, multicenter randomized and controlled studies, with a local application of MAL, followed by red light exposure, and in two multicenter randomized, placebo-controlled studies, with ALA followed by blue

light.^{18,19} Comparative studies have demonstrated that a single MAL-PDT session is more efficacious than a placebo and as efficacious as cryotherapy or topical chemotherapy



FIGURE 65-1 (A) Diffuse grade II/III actinic keratosis of the face. (B) Result after 2 PDT sessions.

with 5-fluorouracil. The percentage of responses was much higher with two separate PDT sessions. In multicenter randomized clinical studies, the clearance rate was 69% if a single treatment session was delivered²⁰ and 83% (vs. 28.7% with the placebo),²¹ 91%^{22,23} and 89%,²⁴ respectively, if a second treatment was delivered 1 week apart. Similar results (89%) were obtained by repeating the treatment after 3 months in patients who had not attained complete remission after the first treatment session.²⁵

In all studies carried out, healing was achieved without scarring and the cosmetic effect was deemed "excellent" by the majority of patients and doctors and definitely better in comparison to cryotherapy or 5-fluorouracil.^{12,20,22–24,26–28} Compared to cryotherapy, two PDT sessions had a superior efficacy to one freeze-thaw cycle, whereas one PDT session was as effective as a double freeze-thaw cycle. Similar efficacy has been demonstrated comparing ALA-PDT with 5-FU but PDT was better tolerated.^{20,23,29}

The skin location of AKs can influence the results. MAL and also ALA-PDT are effective in clearing AKs on the face and scalp; clinical results (87% vs. 76%) and cosmetic outcome (77% vs. 50%) significantly favored PDT when compared to cryotherapy.³⁰ Cosmetic outcomes (excellent or good) of 96%, 97% and 98% were reported.^{20,23,24} Kaufmann et al.³¹ however, showed lower efficacy with MAL-PDT (78%) on the extremities when compared to cryotherapy (88%).

Four studies report the inferiority of response of acral AKs in comparison with facial lesions with weighted clearance rates of 44% (105 of 240) compared with 91% (286 of 315)^{32–35} and scalp lesions (93%) responded better than did facial (87%) lesions.³⁶

Before cream application, a careful lesion preparation with debridement using a sharp dermal curette is suggested for hyperkeratotic lesions because grade 1 lesions had slightly higher complete response rates than grade 2 lesions (89% vs. 80%), and large lesions (diameter >20 mm) had a poorer response compared to smaller lesions.³⁶ In a recent paper, Van Der Geer³⁷ shows that a pretreatment of AKs on the dorsum of the hands with diclofenac 3% gel can improve the PDT efficacy.

A reduced MAL (160 mg/g) incubation period (1 vs. 3 h), in an open, randomized, parallel-group multicenter study showed for lesions on the face and scalp, complete response rates of 78% for thin AKs and 74% for moderately thick AKs after 1 hour versus 96% and 87% after 3 hours incubation, but recurrence rates at 1 year after two treatments were similar (19% with 1 h vs. 17% with 3 h).³⁸

In a double-blinded randomized clinical trial, Wiegell et al.³⁹ highlighted nondifferences in response rates or adverse events, comparing 16% and 8% MAL-PDT to home-based daylight exposure in two symmetrical areas of 30 patients with mostly thin-grade AKs of the face or scalp (complete response rate after 3 months was 76.9% for 16% MAL and 79.5% for 8% MAL), but longer follow-up is necessary. A variety of incubation times and light sources

were used in the numerous studies in the literature but a standardized protocol exists that has shown excellent clinical and cosmetic results.^{6–8,10–14} New developments will contribute to the optimization of this treatment modality, new methods of alleviating pain are of high interest, especially when large areas are treated and a new formulation might contribute to a wider acceptance of the treatment.⁴⁰ Two randomized-controlled phase III studies have investigated the efficacy and safety of a patch (self-adhesive, 4 cm² in size with 8 mg 5-ALA per patch, 4 h application with neither lesion preparation nor bandaging) in comparison with placebo-PDT and cryosurgery in 449 patients with mild to moderate AK lesions of the head and face. The results after 12 weeks showed promising results and 5-ALA patch-PDT proved to be superior to the placebo-PDT (82% vs. 19% and 89% vs. 29%) and to cryotherapy (77%).⁴¹ The use of a 5-ALA patch could improve PDT handling because the patch is applied directly on the lesions without preparing them by curettage; occlusive dressing and light protection are not necessary. However, bigger patches to treat large areas of AK should be evaluated, considering the new concept of field cancerization.

Actinic cheilitis is a subtype of actinic keratosis localized to the lip that mainly involves the lower lip after long-term exposure to the sun. In this critical localization, common therapeutic modalities for actinic keratoses are more difficult to apply, and cure rates of many of these treatments are limited. The major therapeutic approaches include surgical excision (vermilionectomy), cryotherapy, electrodesiccation, CO₂ laser ablation, 5-fluorouracil cream, and 5% imiquimod cream. PDT could be considered a new therapeutic option. The first report about PDT treatment for actinic cheilitis using 5-ALA as topical photosensitizer was published about 9 years ago. From 1996 to date, few papers have indicated an improvement in porphyrin sensitization of the epithelial tissue by using MAL/ALA PDT in actinic cheilitis.^{24,42} From a practical perspective, MAL-PDT can be suitably and safely integrated into clinical practice. Berking et al.⁴³ observed a complete clinical cure in 47% (7/15) and a partial cure in another 47% (7/15) of the treated patients, with excellent cosmetic outcomes and patient satisfaction in most cases. More recently, Rossi et al.⁴⁴ showed the same excellent results with complete response in five patients after two PDT sessions, with a period of 14 days between the first and the second applications, and without recurrences after a 30-month follow-up period.

Severe adverse events have not been reported, however, pain, burning and/or itching in the irradiated areas during and/or sometimes after treatment, especially those localized on the face, are quite frequent and the formation of crusts is always present but these disappear in a few days with a complete and full recovery. Wiegell et al. showed that PDT with MAL was significantly less painful than with ALA but in 20 healthy patients.⁴⁵

In conclusion, PDT represents an effective therapy for thin and moderately thick AKs, particularly for

multiple lesions located on the face and scalp and superiority (in clinical results and cosmetic outcome) to cryotherapy, depending on the protocol. Efficacy is poorer for acral lesions. For very thick keratotic lesions, biopsies should be considered because, even if squamous cell carcinoma is limited to microinvasive involvement, the treatment outcome is poor.⁴⁶ It is well tolerated and noninvasive and there is no need for anesthesia.

Basal Cell Carcinoma

Comparison studies conducted in patients with basal cell carcinoma (BCC) of less than 2 mm depth have shown that PDT, but especially MAL-PDT, is more efficacious than the placebo and as efficacious as surgical excision.⁴⁷⁻⁴⁹ Other studies comparing PDT to cryosurgery for the treatment of BCC have shown at least equivalent efficacy.⁵⁰ In a recent multicenter, randomized study, comparing photodynamic therapy (topical MAL-PDT, a 3-hour incubation time, 75 J/cm² with noncoherent red light at 570-670 nm) with cryotherapy, complete clinical response rates after the 3-month follow-up were 97% for MAL-PDT and 95% for cryotherapy. After the 5-year follow-up, remission rates were almost identical with 75% for PDT and 74% for cryotherapy. Of the lesions initially cleared with MAL-PDT, 22% had recurred vs. 29% after cryotherapy, but cosmetic outcome was superior following PDT (87% vs. 49%).⁵¹

Soler et al.⁵² found no differences in cure rates (82% vs. 86%) comparing laser and a broadband light source when treating superficial BCCs with ALA-PDT, however, filtered broadband lamps or especially light-emitting diodes system offer practical advantages for clinical practice when treating multiple lesions, and are relatively inexpensive and compact. Recently, intense pulsed light (IPL) was evaluated for PDT, but there is a report of a decreased PDT effect compared to broadband light source.⁵³ In a prospective, comparative multicenter phase III study, superficial BCC treated with MAL and irradiated with noncoherent red light (570-670 nm, 75 J/cm²) was again compared to cryosurgery. The 3-year clearance after application of the two modalities was 78% and 81%, respectively.⁵⁰ Moreover, 93% clearance rates were reported when using two consecutive treatments (with a 1-week interval) of MAL-PDT with the same protocol (MAL 3 h, 75 J/cm², 570-670 nm).⁴⁹ MAL-PDT had some other important advantages over conventional therapy: repair occurred rapidly without scarring, there was no bleeding and the tolerability of the therapy was very good, especially for the treatment of multiple or broad-sized lesions, those recurring following surgery or radiotherapy or located in "surgically difficult" areas (face, especially the nose, around the ears, eyes and the genital and perineal area) although special preoperative handling is necessary. Although recurrence is difficult-to-treat, sBCC is high, PDT has shown good efficacy and is a viable alternative when surgery would be inappropriate for the patient or the physician wishes to maintain normal skin appearance.

However, there is apparently great variation in the response to photodynamic therapy of different morphologic types of BCC. PDT has the greatest activity against superficial BCC (Figures 65-2a and b), with topical ALA/MAL achieving complete clearance in some cases with a single treatment session, therefore two treatments 1 week



FIGURE 65-2 (A) BCC before PDT treatment. (B) Clinical result after 2 sessions of photodynamic therapy.

apart have been recommended in the most important guidelines.^{6-8,10-14} Lesional thickness in susceptible tumors must be less than 3 mm.

Nodular BCC, given its vertical growth and thickness, is less responsive to PDT and generally, surgical excision remains the treatment of choice. Early studies of PDT performed over a decade ago showed 3-month clearance rates for superficial BCC ranging from 55-79%, and rates of fewer than 70% for nodular BCC with ALA-PDT.⁵⁴ In a review of 12 early studies, the complete clearance rates of 826 sBCCs and 208 nBCCs with ALA-PDT were 87% and 53%, respectively.⁵⁵ A randomized double-blind controlled design comparing MAL-PDT to a placebo for nodular BCC treatment noted a 6-month clearance rate of 73% in the MAL group versus 21% in the placebo group.⁵⁶ A multi-center randomized trial of the effect of MAL on nodular BCC, compared MAL application for 3 hours occlusion prior to light exposure (570-670 nm, 75 J/cm², 50 to 200 mW/cm²) to surgical excision with a 5-mm margin. The 1-year clearance was noted to be 85% for MAL versus 98% for excision.⁵⁷

Debulking with curettage prior to PDT application was attempted to increase the cure rate of nodular BCC. Persistent BCC clearance was reported at 3 months with persistent resolution maintained at the 36-month follow-up. Treatments involved either a one-time application or a single cycle with two applications 7 days apart. The average clearance rate was 87% in superficial BCC and 53% in nodular BCC.⁵⁸

In an open-label, uncontrolled, prospective multi-center study, MAL treatment achieved 85% clearance of superficial BCC and 75% of nodular BCC at 3 months. At 24 months, the overall BCC clearance was 78% and a near 100% satisfaction with the cosmetic outcome.⁵⁹

Regarding long-term follow-up, a retrospective study examined lesions 35 months after treatment. The initial treatment protocol entailed application of MAL for 3 or 24 hours prior to light irradiation (570-670 nm, 50-200 J/cm², 100-180 mW/cm²) and, 3 years later, clearance was as high as 92% in selected cases.⁶⁰

BCC can have a more complex pathology and shape than AK. To overcome the hurdles involved with treatment of various morphologies of BCC, pretreatment regimens have been used to improve results with thicker tumors. Studies have also been published supporting the effectiveness of PDT for both superficial and nodular BCC, although it was noted that with nodular BCC, appropriate pretreatment preparation is required to enhance effectiveness, which includes removing the exophytic components for BCCs more than 2-3 mm in thickness, and a subsequent retreatment 7 days later.^{60,61}

Penetration enhancers, such as EDTA (ethylenediaminetetraacetic acid) and DMSO (dimethylsulfoxide), have also been suggested as treatment intensifiers and as intralosomal ALA administration but there are no comparative data that demonstrate increased efficacy.⁶²⁻⁶⁴

In a small prospective study, 3 weeks after debulking the tumor, 5-ALA was applied for 6 hours and then irradiated (630 nm, 120 J/cm², 100 mW/cm²), with results showing more than 90% clearance at 3 months.⁴⁸ Therapeutic use of PDT has also been assessed for morphologically complex BCC. In so-called "difficult to treat" BCC, a prospective multi-center noncomparative study found that 3 hours of MAL followed by light exposure (570-670 nm, 75 J/cm²) induced clearance for 2 years in 76% of lesions with "excellent" or "good" cosmetic outcome, rising to 94%. Truncal (88%) tumors responded better than those on the head (54%).^{65,55}

PDT may be a valuable adjuvant treatment for extensive BCC treated with Mohs' micrographic surgery and useful in the treatment of patients with nevoid basal cell carcinoma syndrome (NBCCS).^{66,67}

Pigmented BCC is yet another therapeutic challenge for PDT since the light irradiation associated with PDT does not achieve optimal light penetration into these tumors. Morpheeic BCCs should not be treated with PDT and Mohs' micrographic surgery is the gold standard.⁶⁸ PDT for BCC is generally well tolerated with transient and manageable pain and erythema in most patients.

Bowen's Disease

Bowen's disease (BD) is a form of intraepithelial SCC, and because of its superficial nature, has been one of the cutaneous malignancies for which PDT has been considered most promising. The literature suggests PDT may be a first-line treatment for SCC *in situ* that manifests as large and/or multiple lesions, is inoperable, or occurs in areas expected to heal poorly.⁶⁹ Conversely, for Bowen's disease with an invasive component, PDT may be used as an adjuvant therapy in combination with more definitive surgical treatment.⁷⁰ The therapeutic effects of topical PDT using 20% ALA or MAL have been assessed extensively in the treatment of BD with open (pilot and case series)⁷¹⁻⁸¹ and randomized comparison studies.^{77-79,82-84}

The ALA studies show initial cure rates of 88%, 94%, and 100%, the initial cure rate for MAL was 93%. At the 12-month follow-up, low rates of recurrences were seen with 15% for MAL compared to 21% for cryotherapy and 17% for 5-FU, and 0-12% for ALA compared to 10% for cryotherapy and 18% for 5-FU.^{84,85} ALA/MAL-PDT was found effective in BD, achieving good cosmesis; it had at least a similar efficacy to cryotherapy or 5-fluorouracil but with fewer adverse events. The side effects are mild-moderate, of short duration, and easily managed. A large randomized, controlled, multicenter study reported similar clearance response rates following MAL-PDT (86%), single freeze-thaw cryotherapy (82%) and a 1-month application of 5-FU (83%). Clearance rates after 2 years for MAL-PDT were 68% versus 69% with cryotherapy and 59% with fluorouracil (76%).⁸⁶

More recently, in a retrospective single-center study between 2001 and 2006, Doffoel-Hantz et al.⁸⁷ showed

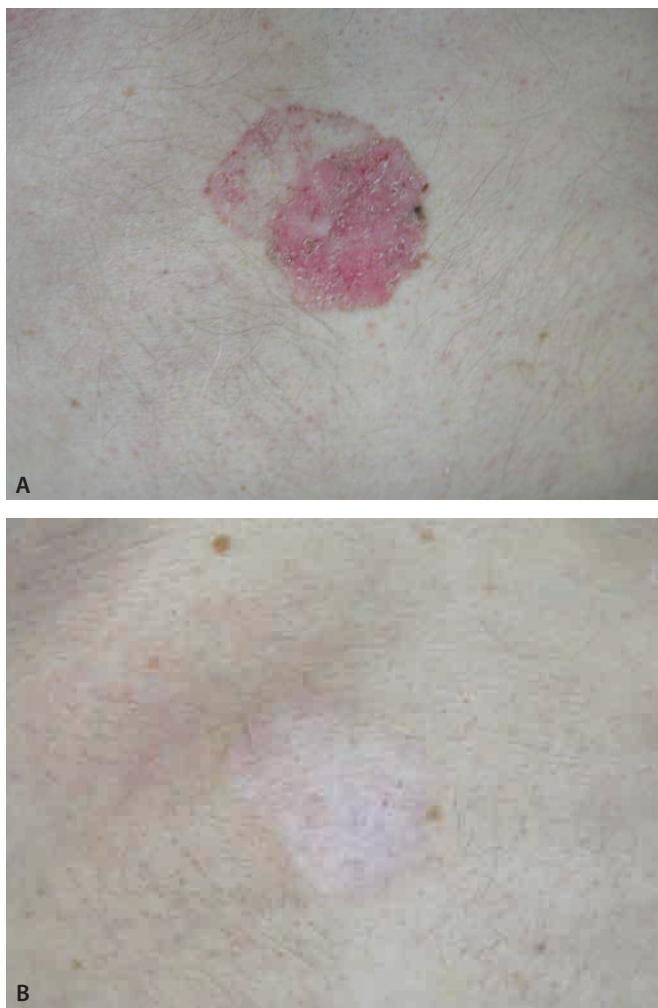


FIGURE 65-3 (A) BD before treatment. (B) Result after PDT.

in 22 patients with a total of 38 cases of BD, a complete remission in all patients at the 3-month follow-up, 100% remission rate at 6 months, 95% at 12 months, and 85% at 24 months, confirming the good efficacy of PDT in the treatment of BD in terms of both clinical remission and cosmetic results. A series of studies have shown PDT to be at least as or more effective than some other topical therapies for BD (Figures 65-3a,b).

Another multicenter randomized-controlled study comparing MAL-PDT to 5-FU and cryosurgery, found 12-month clearance rates of 74%, 65%, and 62%, respectively. The MAL treatment was thus found to be no less effective than the alternative choices.⁴⁶

Morton CA et al.⁷⁷ in an European multicenter randomized study using ALA with a 4-hour application and repeat treatment as required (630 nm, 100 J/cm², 50-90 mW/cm²) observed that there was an 82% clearance with PDT at 1 year compared to a 48% clearance in a group treated with 5-FU. This difference was statistically significant.

A prospective study using ALA with a 4-hour incubation time before light (630 nm, 100J/cm², 70 mW/cm²)

noted complete clearance of 80% of the lesions at 1 year and a suggested efficacy at least equal to that of cryosurgery.⁷⁸

The clearance rate in BD is 82-93% but long-term cure rates are highly variable, depending on different clinical thicknesses, the histologic depth of invasion, and the degree of cell atypia.⁴⁶

These results are comparable to those obtained by Britton and colleagues by using a pulsed dye laser (585 nm) instead of nonlaser light sources with ALA-PDT for the treatment of 17 patches of BD with an 82% complete clinical response.⁸⁸ Recently, a relapse rate of 17% after 64 months was reported, showing an acceptable long-term efficacy comparable with more established therapies.⁸⁹ In immunosuppressed transplant recipients, MAL-PDT was compared with 5-FU with a complete remission of 89% after PDT and 13% after 5-FU following the 6-month follow-up.⁹⁰

Topical PDT may offer advantages over existing modalities for lesions in poor healing sites such as the lower leg, and for penile, digital, and facial lesions where existing treatments have recognized limitations. Therefore, the removal of large BD, multiple lesions, or cancers in surgically "difficult" areas often causes functional loss or cosmetic disfigurements. Treatment is generally well tolerated and relevant adverse effects are not registered. Because of the appreciable nonresponse and recurrence rates, patients should be monitored closely during the first 2-3 years after PDT, which is when most lesion recurrences occur.⁹¹

Treatment of Other Cutaneous Malignancies

A recent report shows that MAL-PDT is equally effective in the treatment of Bowen's disease and microinvasive superficial squamous cell carcinoma SCC, whereas efficacy decreases for infiltrating SCC. Although ALA/MAL PDT has shown efficacy in some studies of superficial SCC, in view of its metastatic potential and high recurrence rates (up to 69%), caution is currently advised in the use of topical PDT to treat this tumor, and surgical excision is the gold standard.⁹²⁻⁹⁴

Pilot studies and cases report highlighted positive findings about the use of PDT in the treatment of early cutaneous T-cell lymphoma (CTCL), although no large-scale studies have been reported and the literature is mostly anecdotal. In the first reported treatment of CTCL, two plaque lesions were treated with 20% ALA cream followed by laser irradiation. PpIX production was demonstrated by real-time laser-induced fluorescence to have a fivefold increase in lymphoma cells over normal cells.⁹⁵ Subsequent studies investigated the possible reasons why CTCL cells could accumulate PpIX, finding that lower intracellular iron levels and competition for iron between ALA-induced heme production and cellular growth processes could be

responsible for selective accumulation and subsequent treatment effectiveness.⁹⁶ In the largest study to date, the Edstrom DW, et al. examined 10 patients with plaque and tumor-stage lesions of mycosis fungoïdes (MF), both from clinical and histologic and immunohistochemical points of view. The protocol was 6-hour occlusive medication with 20% ALA cream followed by red light irradiation of the lesions. After a single treatment, clinical remission was noted in 7 of 10 plaques, with a corresponding regression of infiltrate, lower proliferating cell levels, and a decrease in Ki-67 and CD71. The tumor lesions did not respond. The investigators concluded that there was a good clinical and histologic effect of PDT on local plaque CTCL.⁹⁷ In conclusion, PDT is shown to be useful in treating early CTCL.

Other cutaneous lymphomas, including cutaneous B-cell lymphoma (CBCL), have been treated successfully, but mainly when other treatment modalities have failed or if a particular patient cannot undergo more established therapies.⁹⁸

A retrospective study on extramammary Paget's disease (EMPD) using 5-ALA in repeat applications of 0-4 hours duration prior to light (500-790 nm, 200-400 J/cm², 18-150 mw/cm²) noted complete clearance of 31% of the treated lesions (16 cases) at 12 months. This study noted a possible relation between the likelihood of clearance and the diameter of the lesion; unfortunately, the results of this series were clouded by the inclusion of several cases that had failed prior therapy with alternate approaches.⁹⁹ For the frequent local recurrence and problems associated with extensive surgery, PDT treatment may be justified even if the results do not reach the levels obtained for BCCs, AKs, and BD.¹⁰⁰

Forman Taub,¹⁰¹ referred to a positive experience in the treatment of disseminated superficial actinic porokeratosis (DSAP), but multiple treatments seem to be necessary at the highest light dosages and longest incubations with some pretreatment of the lesions (5-fluorouracil, imiquimod, salicylic acid containing compounds, retinoids, or a combination thereof) to get consistent results. The same author, however, asserts that lesions will recur in 1 to 2 years, leading to the need for annual treatments. We are still in the field of anecdotal experience, thus it is hoped that more case reports and clinical trials will be reported in the future.

Tumor Prevention

The prevention of the incidence of neoplasms represents one of the most important clinical fields of interest in modern medicine and, regarding dermatology, PDT-based clinical action could play a great part in it. In fact, PDT chemoprevention with topical photosensitizing agents could offer a topical therapy for patients that would affect their lives for as long as they live. If PDT can be useful in photorejuvenation, in the rapid and effective treatment

of skin cancer and premalignant conditions, and definitely in the improvement of overall skin health, thus it must be a powerful means of preventing any degenerating skin condition. This could be PDT's most important feature, and continuing research is worthwhile. However, tumor prevention is important, especially for organ-transplant recipients (OTRs), and PDT has become an interesting treatment modality for dealing with NMSC among OTRs who exhibit an increased risk of developing NMSC because of their immune suppression.^{102,103}

Infectious Cutaneous Diseases

The use of PDT for treating infections started in the last few decades when the demonstrated antibiotic resistance required new antimicrobial strategies. In particular, *Staphylococcal* resistance to methicillin and closely related penicillins had been noted since the introduction of penicillase-stable β-lactam antibiotics like methicillin or cloxacillin. Inactivation of ubiquitous species of *Staphylococcus aureus* was studied using photosensitizers such as hematoporphyrin, phthalocyanine, Photofrin, and 5-ALA.

A novel porphyrin-based photosensitizer, XF73, showed high efficacy at killing methicillin-resistant *Staphylococcus aureus* (MRSA) without damage to keratinocytes or eukaryotic cells. PDT with this photosensitizer could serve to prevent MRSA infection in hospitals as well as for in burns or other open wounds.¹⁰⁴ An in vivo animal model of *Staphylococcus aureus*-infected mouse bone successfully treated with PDT, seems to suggest the future role of this technique as a good alternative treatment for osteomyelitis.¹⁰⁵

Mice with a severe combined immunodeficiency developed mucocutaneous candidiasis that was treated successfully with methylene blue and 664 nm diode laser in a dose-dependent fashion. This led the investigators to conclude that this particular PDT modality could be a possible treatment option in humans suffering from Candidiasis.¹⁰⁶ In a recent paper, an interdigital tinea pedis treated with PDT (29% ALA in Eucerin cream and 75 J/cm² red light) was completely resolved, but four of the nine patients had a recurrence of the disease within 4 weeks of therapy.¹⁰⁷

The most relevant results are reported for the treatment of viral infections, especially for immunosuppressed patients. The new indications for PDT include many types of viral infections that are related to the human papilloma virus (HPV), such as verrucae, condylomata acuminata, and periungual warts and widespread distributed as epidermodysplasia verruciformis (EV). The diagnosis is often straightforward, but the treatment is difficult and lengthy. Simple and currently employed medical treatments such as keratolytic agents, curettage, glutaraldehyde, and invasive methods such as cryotherapy or electrosurgery and laser therapy have shown good therapeutic effect.

Still, some warts remain resistant, and immunosuppressed patients or those under immunosuppressive therapies especially need new treatment modalities. Some pilot studies have demonstrated that PDT might be an additional option in the treatment of cutaneous and mucosal HPV-infections alone or combined with conventional modalities to reduce recurrence rates. Warts or condylomata treated with PDT have demonstrated good results. Other viruses not related to HPV treated with PDT that have been reported include molluscum contagiosum and herpes simplex. PDT can be used successfully to inactivate pathogens from blood products before infusion.¹⁰⁸ Treatments of verrucae are often discouraging to both the patient and clinician: therapeutic options for these clinical lesions can be found in every textbook and in numerous papers. They usually focus on the physical destruction of the lesion and treatments include cryotherapy, curettage, excision, carbon dioxide laser ablation, pulsed dye laser therapy, liquid nitrogen, electrosurgery, and the application of a variety of topical acid preparations, but many other modalities have also been reported in the literature. However, some warts remain resistant to the therapies. PDT has been reported in the treatment of recalcitrant verrucous lesions and molluscum lesions over the past 10 years, with good results. However, many papers report that the oil-in-water emulsion containing the photosensitizer was enriched with additives such as 2% ethylenediaminetetraacetic acid and 2% dimethyl sulfoxide. Dosing the correct regimen of light energy exposure and choosing the right mixture of sensitizer, ALA-PDT may represent a useful modality for recalcitrant verrucae and molluscum.^{109,110}

Its emerging antiproliferative and antimicrobial effects may have other uses in medicine and those areas of research identified appear to be promising for some new applications that may become useful in the future in clinical practice. Especially PDT may have a place in treating leg ulcers and cutaneous infections, and it may also reduce requirements for systemic antibiotics in the management of leg ulcers, thereby lessening antibiotic resistance. In 1990, it was demonstrated that *Escherichia coli* could be killed if pretreated with methylene blue and exposed to light and *Helicobacter* infection was eradicated with methylene and toluidine blue. New photosensitizers have shown a high efficacy at killing methicillin-resistant *Staphylococcus aureus* (MRSA) without damage to keratinocytes.¹⁰⁴ The investigators have postulated a use for this therapy to prevent MRSA infections in hospital, as well as for burns or other open wounds especially in immunocompromised hosts. The interesting notice is that the varied organisms tested do not seem to have been capable of mounting a defense or developing resistant strains to PDT.¹¹¹

Photodynamic inactivation of microorganisms is based on the concept that the photosensitizer should be localized, preferably in the bacteria and not in the surrounding tissue or cells, and subsequently activated by low doses of visible

light of an appropriate wavelength to generate free radicals and singlet oxygen, as mentioned above, that are toxic to the target microorganisms.

In leg ulcers, an increase from 24% to 50% oxacillin resistance in *S. aureus* and from 9% to 24% ciprofloxacin resistance in *P. aeruginosa* has been demonstrated and in superficial wounds, an increase from 24% to 36% ciprofloxacin resistance in *P. aeruginosa*.¹¹² This data demonstrates the rapid increase of antibiotic-resistant bacterial pathogens because of the systemic use of antibiotics in dermatology and highlights the importance of searching for alternatives. Photodynamic therapy could be a very important antimicrobial alternative because of the availability of a broad spectrum of photosensitizers that have shown significant antibacterial activity against gram-positive and gram-negative bacteria, for its applicability against antibiotic-resistant bacteria, independent from their antibiotic resistance pattern, which is important for the repeated treatment of chronic and/or recurrent infections. It determines the lack of induction of resistance after multiple treatments and the lack of mutagenicity as well. Recently, Clayton et al.¹¹³ showed dramatic wound improvement using 5-aminolevulinic acid-PDT, with significantly less infection and negative swabs for MRSA in a woman with a chronic recalcitrant venous leg ulceration that had been unresponsive to conventional treatments and complicated by several episodes of cellulites with eventual methicillin-resistant *Staphylococcus aureus* colonization. PDT is being clinically studied for other dermatologic infections such as leishmaniasis. Cutaneous leishmaniasis (CL) represents one of the most serious skin diseases in many developing countries and standard treatment are often ineffective, expensive, or yield poor cosmetic outcome. Pentavalent antimonial drugs are the first-line therapeutic agents but many different treatments have been described for Old World cutaneous leishmaniasis (OWCL) and some clinical reports have shown promising results by using PDT. Gardilo et al.¹¹⁴ compared the efficacy of PDT (MAL and 75 J/cm² red light) to paromomycin sulfate in 10 lesions of CL obtaining complete response in all PDT treated lesions versus two paromomycin treated plaques. Ten months after the last treatment session, there were no clinical signs of recurrence and healing and cosmetic outcome was excellent. Asilian and Davami reported,¹¹⁵ in a placebo-controlled, randomized clinical trial, complete response in 93.5% of patients treated with PDT versus 41.2% and 13.3% treated respectively with paromomycin and placebo. At the same point (2 months after the end of treatment), 100%, 64.7% and 20% of the lesions had parasitologic cure in groups 1, 2 and 3 respectively. Therefore, data are still limited, PDT cannot at this point be recommended in routine clinical practice, and additional controlled trials need to be performed in order to develop a better evidence-based approach.¹¹⁶ The study of photodynamic therapy in this area over the next several years seems to be very bright.

Inflammatory/Immunologic Disorders

The rise in antibiotic-resistant strains, reduces the future usefulness of current mainstay therapies and the use of ALA-PDT in the treatment of moderate to severe inflammatory acne vulgaris, and has received a great deal of publicity recently as a novel therapy. Although acne vulgaris therapy has been studied, using different photosensitizers, incubation times, and various light sources, the most effective treatment regimen for ALA-PDT in acne, therefore has not been established. An open randomized-controlled study by Hongcharu et al.¹¹⁷ using a broadband light source (550–700 nm), and a 3 hour ALA drug incubation time, demonstrated significant clearance of the lesions after 4 weeks that persisted up to 10 weeks in patients who received a single treatment and up to 20 weeks in those who had received multiple treatments. Adverse effects consisted of an acneiform folliculitis, postinflammatory hyperpigmentation, superficial peeling and crusting. The efficacy of ALA-PDT and the possible mechanism of action in acne were confirmed and presented by Pollock, but using a diode laser.¹¹⁸ Similar results, but at one-third of the fluence and as a single treatment were reported previously for an intractable case of acne vulgaris; the treated area remained disease-free for 8 months.¹¹⁹ A second study by the same authors of 13 patients using a single treatment of polychromatic visible light source (600–700 nm), showed good improvement (61.8% at 3 months) and a 6-month follow-up period with a reduction in new acne vulgaris lesions and they favor this light source because it is cheaper, quicker, and provides more uniform illumination than laser light.¹²⁰ Goldman first reported a short-contact (1 h drug incubation) experience with ALA, using either an IPL or blue light source in the treatment of acne vulgaris and sebaceous gland hyperplasia with “relative” clearing in all of the subjects evaluated and no PDT effect.¹²¹ Similarly, Gold reported a 60% improvement in acne (compared to 43% reported with blue light alone; eight treatments over 4 weeks) for ten patients with moderate to severe inflammatory acne vulgaris, using short contact (30-min drug incubation). The use of an IPL device with ALA in 12 individuals utilizing short contact, full-face therapy, showing a clearance of 72% in those patients with moderate to severe inflammatory acne vulgaris, and no adverse effects. These results were reviewed recently by the same authors.¹²² A study of 14 patients utilizing an IPL device in split-face acne analyses showed that the IPL plus ALA worked better than the IPL alone in treating inflammatory acne vulgaris (87.7% vs. 68.8% on PDT vs. IPL).¹²³ Recently, the use of MAL and red light was reported in a group of patients with inflammatory acne vulgaris with a 68% reduction of acne vulgaris lesions versus no change in the placebo group. All of the patients complained of moderate to severe pain during the treatment, severe erythema from the treatment along with pustular eruptions (lasting 2/3 days), and epithelial exfoliation in most patients. The same authors

showed no significant differences between MAL and ALA after a 3h incubation time in the improvement of inflammatory counts and no change in noninflamed lesions.¹²⁴

An interesting paper reporting on 2-3 PDT-treatments (at 2-week intervals) in short therapy (90 min.) showed good clinical results for the inflammatory component of acne at the 12-week follow-up in 16 patients with moderate to severe acne, by using MAL but at a 4% concentration. All the patients reported a slight but tolerable sensation of heat during the illumination, followed by slight erythema (which disappeared within 48 hours in 14 patients, and within 5 days in the two patients with phototype II skin) and modest scaling that began approximately 3 days after the treatment.¹²⁵ As in the study by Wiegell and Wulf,¹²⁴ no difference was noted in the noninflammatory lesions at the 12-week follow-up, whereas the count of inflammatory lesions had decreased on average by 66% (range 56–81%). They conclude that the use of MAL reduced to a 4% concentration, together with the application of low doses of light (10-20 J/cm²), may be useful for controlling the side effects of PDT in acne and have the same efficacy as the higher concentration but with lower costs.¹²⁵

In conclusion, researchers have been studying the effects of ALA on active acne vulgaris, and the results have been very encouraging to many in the dermatologic community, but it is evident that much of the literature data does not provide a gold standard level of clinical evidence, supporting the use of PDT in acne and controlled studies on a larger number of patients are needed in order to optimize the PDT parameter for acne, and the most effective therapy capable of balancing good efficacy with reduced side-effects.¹²⁶

There is a fair amount of literature about PDT and psoriasis that deals, in part, with the results, and, in part, with whether PDT is a practical or useful alternative for treatment. Bissonnette and colleagues¹²⁷ administered oral ALA at different concentrations (5,10,15 mg/kg) to psoriatic patients, and evaluated protoporphyrin IX (PpIX) fluorescence in lesional and normal skin, as well as in the inflammatory cells, demonstrating a ten-fold increase in fluorescence in the psoriasis over the normal skin at 3 to 5 hours after administration of a single oral dose, with the best clinical improvement observed in a patient who received 10 mg/kg. The same authors demonstrated that systemic PDT induces apoptosis in the lesional T-lymphocytes in psoriatic plaques. Boehncke et al.¹²⁸ showed that both PDT with red light and psoralen plus ultraviolet A light (PUVA) therapy exhibit a similar inhibitory effect on IL-6, TNF-a, and IL-1 secretion in a dose-dependent manner in mono-nuclear cells in psoriatic patients.

Moreover, in everyday practice, it is almost impossible to administer ALA orally because of the concerns about ALA clearance, photoexposure, persistent fluorescence, and subsequent long-lasting photosensitization of the subject. Thus, clinical trials were instituted and showed good improvement of the psoriatic plaques by using topical

5-aminolaevulinic. Even if improvement of clinical psoriasis with PDT has been observed in most studies, after a very thorough review of the literature, the major limiting factor has been the side effects during irradiation of pain and burning sensations. Other disadvantages of PDT are its treatment cost and the partial clearance of lesions. In addition, koebnerization secondary to PDT-induced inflammation was observed.¹²⁹ This highlights the need for other photosensitizers with better tolerability profiles.¹³⁰ Recently, Salm et al. evaluated in a single-blind study, the use of topical 0.1% methylene blue (MB) hydrogel and 565 mW light emitting diode at 670 nm in patients with resistant plaque psoriasis. Sixteen patients experienced complete clearance of their treated lesions, their skin appeared normal in color, texture, and pliability with no complications indicating a lack of skin sensitivity. Histopathologic examinations showed nearly normal epidermis at the end of all sessions.¹³¹ The results are encouraging for the acceptance of MB as a photosensitizer for PDT, as well as a safe and effective method for the treatment of selected cases of resistant localized psoriasis.

Localized scleroderma that is resistant to PUVA seems to respond well to PDT. Cultured keratinocytes subjected to PDT appear to produce increased levels of IL-1, TNF, and matrix metalloproteinase-1 and -3: these could be responsible for the observed antisclerotic effect of PDT.¹³² Another study found a dosimetry range that reduces tissue contraction and collagen density without damage to the keratinocytes, which may prove helpful as an adjuvant treatment for keloids.¹³³

Some authors have tried to treat alopecia areata by means of PDT, also because observations of fluorescence microscopy have revealed diffuse uptake in the epidermis and sebaceous glands.¹³⁴ However, no fluorescence was seen in the hair follicles or the inflammatory infiltrate surrounding the epidermis, and no significant results were seen, showing that PDT is not a successful therapy for alopecia areata.

An interesting study in six vitiligo patients showed a perifollicular pigmentation after the first session and almost double the repigmentation was observed after second session. At the end of the therapy, partial repigmentation of the lesions was observed in four of the six patients.¹³⁵

Photorejuvenation

Aging is a complex and multifactor process that occurs in all individuals at a variable rate, influenced by genetic, environmental, and hormonal factors, which result in several functional and aesthetic changes in the skin. It is manifested clinically by fine and coarse wrinkling, roughness, dryness, laxity, shallowness, pigmentary mottling, teleangiectasias, and, in some cases, with preneoplastic and neoplastic changes. Recently, increased physician expertise, with a view to expanding PDT applications, has introduced

its use for improving visible signs of photoaging ("photodynamic photorejuvenation"). In the initial experiments, ALA-PDT with a blue light source showed high clinical scores for photorejuvenation.¹³⁶

By combining the photothermal effects of pulsed light with the photochemical effects of PDT, an enhanced cosmetic effect has been demonstrated. Ruiz Rodriguez et al.¹³⁷ found that ALA-PDT using IPL as a light source (two treatments at a 1-month interval) resulted in higher levels of qualitative improvement of signs of photoaging in the skin. Goldman et al.¹³⁸ reported similar results with ALA-PDT by using blue light as the light source but with a 1-hour preincubation. The use of shorter incubation times permits improved patient tolerance during treatment and, consequently, fewer adverse effects.¹³⁹ A comparative study with short-contact (30-60 min) ALA-PDT with IPL activation by comparing ALA-PDT-IPL with IPL alone in thirteen patients and 3 months after the final treatment, showed a higher improvement on the ALA-PDT-IPL-treated side than on the IPL-alone side with crow's feet appearance (55% vs. 28.5%), tactile skin roughness (55% vs. 29.5%), mottled hyperpigmentation (60.3% vs. 37.2%), erythema (84.6% vs. 53.8%) and AK clearance rate, the end stage of the skin ageing process, was 78% versus 53.6%.¹⁴⁰ Similar results, comparing IPL alone and ALA-PDT-IPL, were reported by Dover et al.¹⁴¹ that shows an improvement in hyperpigmentation of 65% for IPL alone versus 95% for ALA-PDT-IPL and an improvement in fine lines of 20% for IPL alone versus 55% for ALA-PDT-IPL. Similarly, ALA-PDT alone was found to result in greater improvement in photorejuvenation than pulsed dye laser (PDL) alone.¹⁴²

More recently, an improvement in mottled hyperpigmentation, fine lines, roughness and shallowness of the skin was observed by using MAL cream under occlusion for 3 hours before exposure to 37 J/cm² of red light (2 treatments with a 1-month interval), but deep wrinkles, telangiectasias, facial erythema, and sebaceous gland hypertrophy did not change. The authors reported a novel mechanism for evaluating the effect of PDT on skin thickness using echographic analysis.¹⁴³ Similarly clinically obtained results could be evaluated by using optical coherence tomography (OCT), a noninvasive diagnostic method, which gives a histomorphology evaluation of the skin, while avoiding a biopsy and a histomorphology evaluation of the skin after 45 days from the last control.¹⁴⁴

These experiences show how the topical application of ALA/MAL acid followed by well-tolerated light sources (broadband and LED lamps or IPL), can be considered a new noninvasive procedure for the treatment, with minimal side effects, of photoaging skin, and bridges the world of medical and cosmetic dermatologic surgery.¹⁴⁵

Moreover, PDT could be combined in conjunction with other nonsurgical methods for skin rejuvenation, increasing our patients' satisfaction rate, and is relatively easy for any practicing dermatologist to adopt.¹⁴⁶

CONCLUSION

ALA/MAL PDT therapy shows great efficacy and high tolerability for the treatment of nonmelanoma skin cancer, especially in patients with large and multiple lesions, in poor-healing sites and patients immunosuppressed or with comorbidities. The advantages are linked to its selectivity for tumoral cells, its efficacy in treating field cancerization, and the capacity to preserve normal tissues that lead to very

excellent cosmetic results, thus offering a good therapeutic alternative to standard treatment options. In addition, PDT has been used widely and with great success for many off-label diseases and in cosmetic dermatology but further and larger prospective studies with long-term follow-up are required to verify its efficacy and safety in treating those conditions. In addition, possible advancements could be obtained, thanks to the future availability of new sensitizers and new treatment strategies.

What We Know

- The prevalence of AKs continues to rise throughout the world and the level of attention paid to it must be increased from a diagnostic and a preventive point of view.
- Treatment not only of the lesion but also of the “field cancerization” is part of an optimal strategy, aimed at resolving both the clinically obvious alterations, as well as those of the surrounding skin that probably is already the site of genetic alterations and of an initial, gradual replacement of normal cells.
- Among the therapeutic options available, it is advisable, when supported by the clinical situation of the lesions and the patient (numerous lesions and without serious hyperkeratotic phenomena), to favor those options whose objective is the treatment of both the lesion and the surrounding field.
- PDT is a treatment of choice for nonpigmented grade I to III actinic keratosis, especially for diffuse lesions, where it is important to treat the lesion and the cancerization field.
- PDT can be an effective noninvasive method to treat actinic cheilitis of the lower lip.
- PDT has demonstrated long-term efficacy in sBCC, offering excellent or good cosmetic outcomes and an advantage in the treatment of extensive, large, and multiple lesions.
- There is a variation in the response to PDT based on the morphology of the BCC and the thickness of the lesion.
- PDT has demonstrated efficacy in nBCC, offering excellent or good cosmetic outcomes; because of the appreciable recurrence rates, patients should be monitored closely.
- “Difficult to treat” sBCC and nBCC may benefit from pretreatment regimens including debulking and penetration enhancers.
- Given the superficial nature of SCC in situ (BD), PDT shows promise as a first-line treatment for multiple or large lesion SCC in situ, those that are inoperable or expected to heal poorly. It is particularly useful in immunosuppressed transplant recipients.
- For Bowen’s disease with an invasive component, PDT may be used as an adjuvant therapy in combination with surgical treatment.
- The ability of PDT to alter the course of other cutaneous malignancies, immunologic, inflammatory, and infective diseases is at an exploratory stage and clinicians need to combine resources and strengths to optimize PDT for these conditions.
- PDT can be considered a new noninvasive procedure for the treatment, with minimal side effects, of photoaging skin and is able to bridge the world of medical and cosmetic dermatologic surgery. PDT could be combined in conjunction with other nonsurgical methods for skin rejuvenation.
- Never forget that prevention is the best medicine.

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Skin Substitutes

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INTRODUCTION

Skin has a number of diverse and complex functions including sensory perception, thermoregulation and fluid homeostasis¹. Importantly, it also represents the first physical and immunological protection the body has against both pathogenic attack and environmental stress. Chronic or acute damage to the protective barrier function of the skin leaves the body vulnerable to illness and even death. Additionally, extensive or prominent scarring due to poorly healed wounds can result in poor functionality and pain. Of equal importance is the emotional and psychological burden that cutaneous scarring can leave a patient with long after the physical wound has closed^{2,3}. Due to their nature and current treatment strategies the monetary and temporal consequences these wounds impose on the health industry is significant. For example, in the UK alone, treatment of the various forms of chronic ulcers is calculated to cost the NHS in excess of £1 billion a year⁴. Extensive thermal trauma is less common in economically developed countries, such as the UK, but remains of high importance due to the extremely painful nature of these injuries and continued high mortality rates.

Skin substitutes are now a common tool employed by surgeons and clinicians to modify the wound healing process, typically accelerate, in acute and chronic wounds. The main aim being to restore tissue integrity and improve the functional and/or aesthetic outcome of healing. The term ‘skin substitute’ encompasses a range of materials and formats. Substitutes can be categorized in terms of the origin of the scaffold material, such as biological or synthetic, whether they are cellular or acellular, and upon the origin of any cells or tissues used i.e. allogeneic, autologous or xenogeneic. These can then be further subdivided into epidermal, dermal and bilayer substitutes (Figure 66-1). As could be speculated from the number of categories involved, skin substitute design is diverse and continues to diversify as new technologies and techniques immerge and gain prominence.

The goal of skin substitutes is to recreate the anatomy, physiology, mechanical properties and aesthetic nature of the skin prior to damage. There are currently over 20 commercially produced skin substitute materials and numerous more in various stages of product development⁵. The use of these products has led to variable degrees

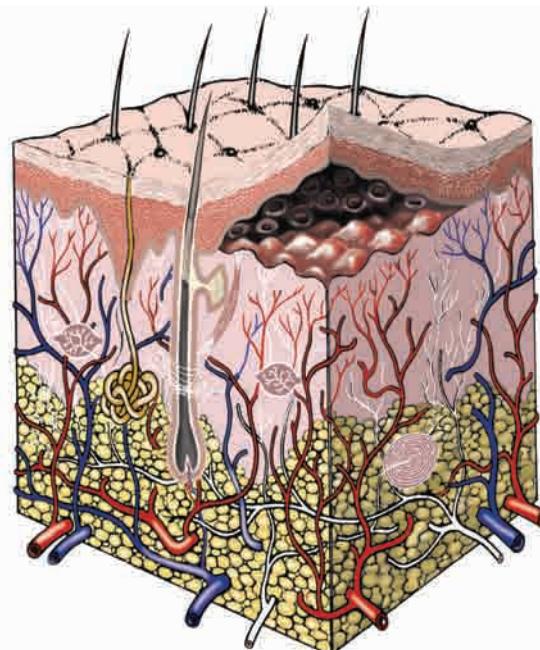


FIGURE 66-1 Structure of the skin with epidermis peeled away to illustrate the dermal papilla.

of improvement in the treatment of chronic and acute wounds.

In clinical studies into how skin substitutes modify the healing process a wide selection of experimental processes and outcomes have been used to assess success, including re-epithelialization, graft ‘take’, immuno-compatibility, mechanical properties and dermo-epidermal junction regeneration⁶. Selective presentation and analysis of these criteria often leave the reader with an incomplete picture of dermal and/or epidermal regeneration, exacerbated by divergent starting wound conditions and defect causes⁶. Often it is the qualitative morphological examination and characterization of the regenerated tissue, particularly dermis, which is crucially overlooked in favour of a quantitative assessment of wound closure, typically time.

Due to the above and the diversity of skin substitutes available there is a level of uncertainty over their effectiveness in comparison to standard wound management strategies in various applications. Evidence-based medicine categorizes the level of evidence available on the clinical efficacy of a treatment or product on the basis of the quality

TABLE 66-1—Levels of Evidence

LOE-1	Systematic review (SR) of Randomised clinical trials (RCTs) High quality RCT
LOE-2a	Low quality RCT SR of cohort studies
LOE-2b	Cohort study/Non-randomised controlled trial
LOE-3	SR of case control studies Case control study
LOE-4	Case series Low quality cohort study/Non-randomised controlled trial Low quality case control study
LOE-5	Case reports Expert opinion without critical appraisal/based on physiology/bench research or 'first principles'

Adapted from Oxford Centre of Evidence Based Medicine⁷

of the research conducted. This allows a clear interpretation of available data which will ultimately aid in developing optimal clinical practice⁷ (Table 66-1). Rather than providing a comprehensive list of clinical studies, this article aims to use an evidence based approach to evaluate and highlight the important findings when using current skin substitutes on a range of cutaneous defects.

NORMAL SKIN STRUCTURE AND FUNCTION

Structurally, the skin can be divided roughly into two distinct layers; the stratified epidermis and dermis. These are separated by a specialized membrane structure termed the basement membrane. Below the dermis is a subcutaneous fatty layer called the panniculus adiposus. This is separated from the rest of the body either by a vestigial layer of striated muscle, the panniculus carnosus in a few anatomical locations or by fascia in the majority⁸ (Figure 66-1). The different structures of the epidermis and dermis reflect the different, but synergistic, roles of the layers.

The epidermis primarily acts as a barrier against environmental insult including UV radiation, air pollution, pathological microorganisms, and toxic chemicals. The squamous, layered 'bricks and mortar' structure of the epidermis reflects this. Its effectiveness largely depends on maintaining the integrity of the stratum corneum, the epidermis' outer most layer. Whilst the epidermis provides a physical barrier, the dermis provides the skin with mechanical strength, elasticity and some body heat insulation⁸. The mechanical properties of the dermis are achieved through high densities of collagen and elastin fibers, with collagen constituting around 77 % of the dry weight of the entire skin⁸. The dermis houses much of the cellular complexity of the skin and contains important structures such as hair follicles and sweat glands.

The epidermis itself is an avascular layer that is predominately composed of keratinocytes (~95 %) and

approximately 0.1-0.2 mm thick⁸. Over the majority of the body, epidermis can be further subdivided into four strata (inner-most first); stratum basale, stratum spinosum, stratum granulosum and stratum corneum. In palmoplantar epidermis a fifth transitional layer, the stratum lucidum, is seen between stratum granulosum and stratum corneum (Figure 66-2)⁸. These layers are generated by the cycling of keratinocytes undergoing gradual differentiation or maturation from the basal layer outwards towards the stratum corneum where they are eventually sloughed off (desquamated). In normal skin this entire process takes 52-75 days⁸. This continuous cycling of cells means that cells damaged by radiation, chemical or physical insult are cyclically removed, preventing the accumulation of damage that could result in disease, e.g. cancer.

Besides keratinocytes, the epidermis contains three other cell types, termed immigrant cells, that substitutes to date have failed to incorporate. These cells migrate into the skin early in development and have specialized roles in protection and sensory perception. Pigment (melanin) producing melanocytes migrate from a position adjacent to the spine during embryonic development⁹. They are found in the basal layer of the epidermis at a ratio of 1 melanocyte for every 35 keratinocytes¹⁰. Sensory Merkel cells are also found in this layer of the epidermis and are common in the glabrous palmoplantar skin and the lips. They are associated with the ends of sensory nerves and are responsible for our delicate sense of touch in the skin. Dendritic Langerhans cells are found in the stratum spinosum and are the first defense against pathogenic bacteria and viruses that attack the skin⁸. Epidermal substitutes rely on repopulation of the replaced skin by these native cells as the graft becomes integrated into the host tissue.

The basement membrane, a specialized structure situated at the dermal-epidermal junction, is a crucial component in the creation of a clinically successful skin substitute^{11,12}. Functionally, the basement membrane anchors the epithelium to the loose connective tissue of the underlying dermis, serves as a partial barrier against the exchange of cells and large molecules between the dermis and epidermis⁸, provides an mechanically scaffold that facilitates tissue repair^{6,13,14} and promotes the differentiation of endothelial precursors¹⁵. The membrane is comprised of the basal lamina, predominately a collagen type IV mesh with proteoglycan and glycoproteins attached, and the lamina reticularis. The lamina reticularis, mainly composed of fibronectin, is attached to the basal laminar through collagen type VII and fibrillin fibrils. Maintaining the connection between the two layers is achieved through adhesion molecules, such as integrins, expressed by the basal keratinocytes and papillary fibroblasts. The expression of specific sets of these molecules can be used to identify cells from this region in a mixed population. The lamina reticularis also contains elastic components which mainly consist of bundled fibrillin microfibrils. These extend into the dermis and entangle with elastin fibrils. These elastic molecules

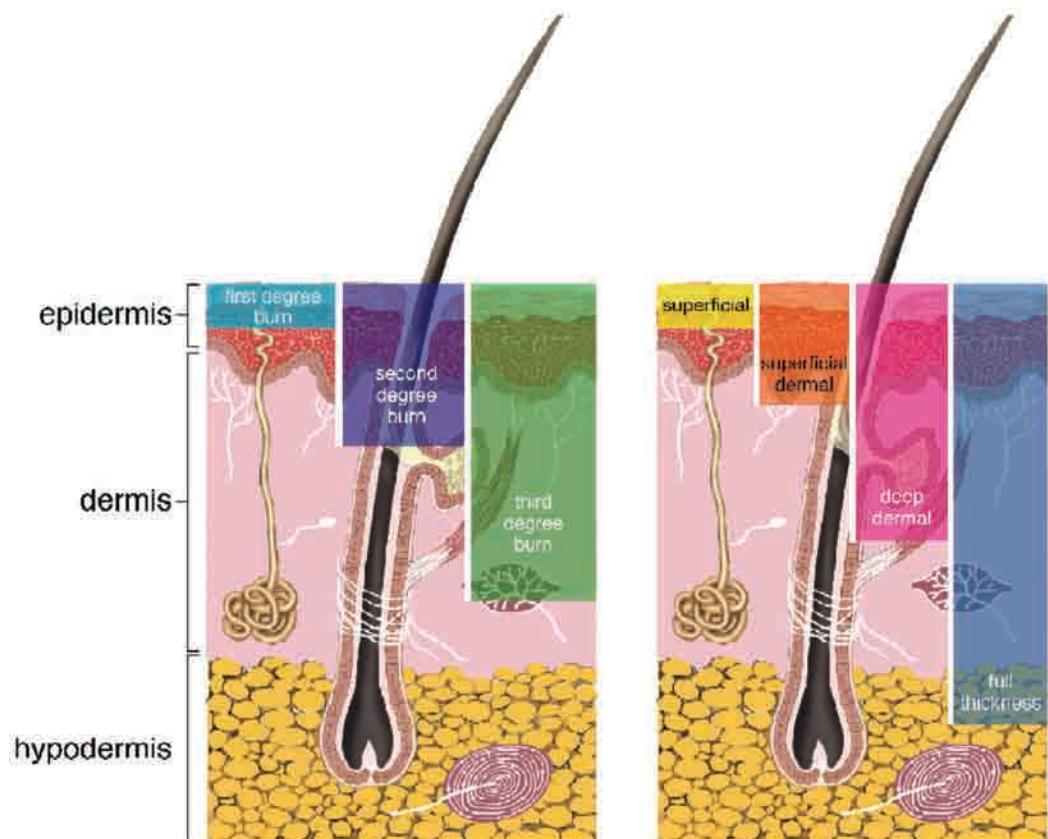


FIGURE 66-2 Classification of cutaneous wound based on depth of wound.

allow the skin to return to its original shape after stretching or contracting and importantly considerably enhance the load bearing ability of the skin⁸. The establishment of a strong epidermal-dermal junction is particularly challenging in skin injuries crossing into the dermis, thereby destroying the native basement membrane necessitating reconstruction.

Mechanical failure of the dermo-epidermal junction in wounds that incorporate engineered material is common^{6,16-21}. Any skin defect is exposed to mechanical forces that may in this case put strain on the attachment of graft to wound bed. These forces can take the form of exogenous normal and shear forces as a result of clinical handling, and shrinkage stresses e.g. due to graft contraction or dehydration^{6,22}. Various hypotheses have been postulated as to why failure at the basement membrane region is observed, particularly when using cultured epithelial autografts including lack of rete ridge formation^{6,18,23-25} and lack of a mechanically sufficient bond between sub-epidermal collagen and anchoring fibrils in the basement membrane^{19,26} (LOE-5). The latter of which is widely accepted as the responsible model⁶.

The main cellular component of the dermis is the fibroblast. These cells produce and secrete large amounts of extracellular matrix (ECM) components, mitogenic and modulatory cytokines, growth factors, and paracrine and autocrine signaling molecules²⁷. The dermis also includes mast cells and, monocytes and macrophages (histiocytes). The dermal cells are supported by a matrix that is mainly

composed of the fibrillar collagens I, III and V. These are organized spatially by the non-fibrillar collagens VI, IX and XIV²⁸. Proteoglycans and glycoproteins are also essential components while elastin provides the matrix with a degree of elasticity and flexibility.

The dermis can itself be subdivided into the papillary (uppermost) and reticular dermis. The uppermost portion of the papillary dermis undulates with the epidermis forming projections of dermis into the epidermis (papillae) and of epidermis into the dermis (Rete ridges). The reticular dermis is the thicker of the two dermal strata and contains structures such as the hair follicle root, sebaceous glands, blood vessels and sweat glands. It is composed of dense irregular connective tissue.

CUTANEOUS WOUND HEALING

Following cutaneous injury, the tissue repair events of the wound healing process have been basically separated into three overlapping stages: inflammation, tissue formation and tissue remodeling^{28,29} (Figure 66-2). Hemostasis, the first stage, is achieved through the formation of a fibrin-rich clot via platelet aggregation and blood coagulation (Figure 66-3). Platelet aggregation relies on their adherence to matricellular proteins exposed in the wound and produced by platelet activated fibroblasts through α IIb β 3 integrin³⁰. Activated platelets release α -granules and growth factors that stimulate fibroblasts to produce ECM components and construct a provisional matrix³¹. The coagulation of

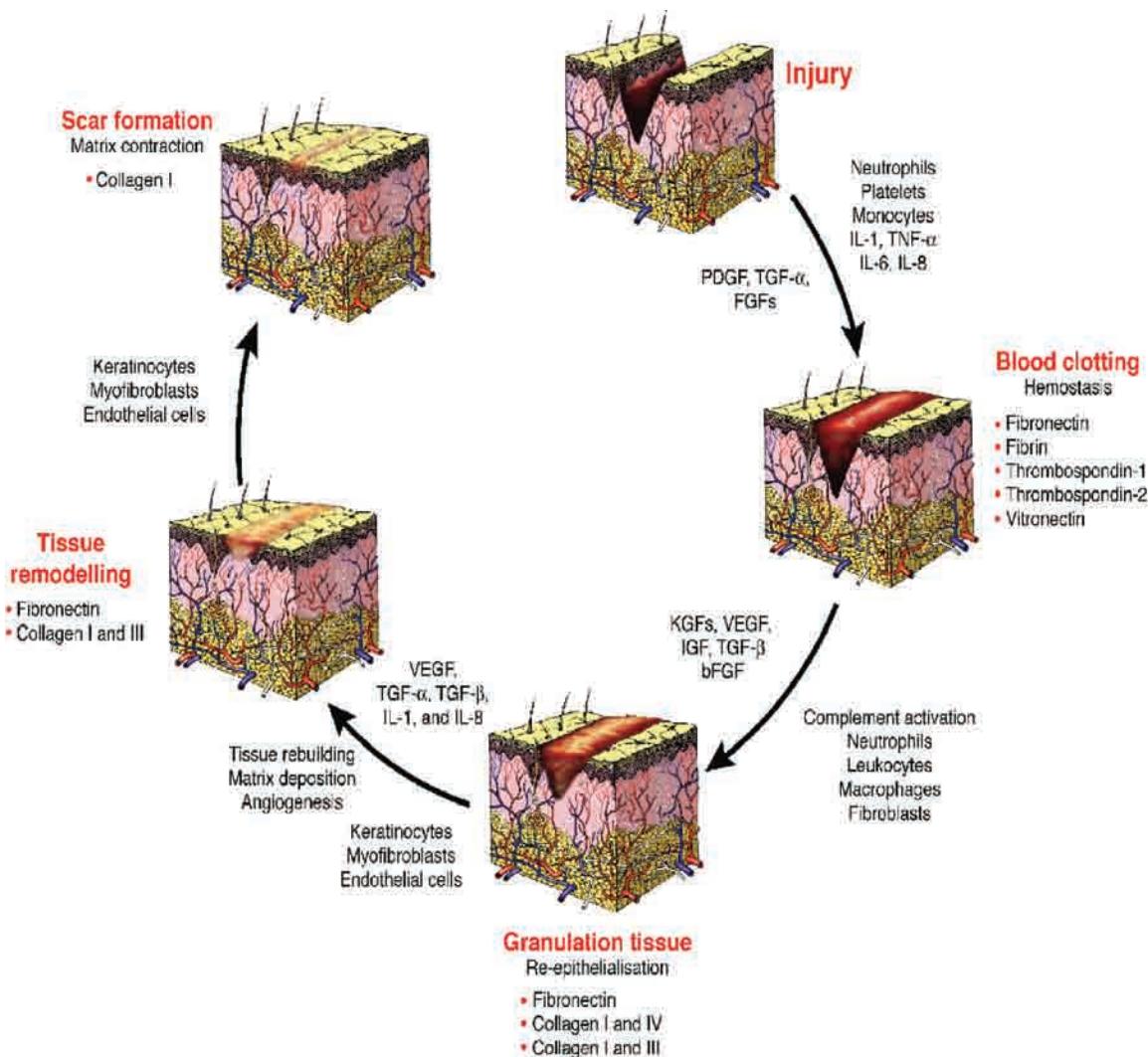


FIGURE 66-3 Wound healing stages with corresponding growth factors and cytokines.

the blood in this way also activates complement pathways, recruiting inflammatory leukocytes to the wound site^{32,33}. Infiltrating neutrophils destroy foreign particles and bacteria through the release of enzymes and reactive oxygen species³³. Monocytes mature into either inflammatory or reparative macrophages and express TGF- α , TGF- β , platelet derived growth factor (PDGF) and insulin-like growth factor-1 (IGF-1)^{33,34}. These growth factors are important for initiation of tissue formation. Prior to the addition of a skin graft or skin substitute the blood clot and provisional matrix is removed through surgical debridement. This step removes non-viable tissue from the wound and any physical barriers to cell migration that exist. This step also helps to clean the wound and prevents infection post-grafting.

The cells of the skin graft initially obtain nourishment through a process called plasmatic imbibition, where the graft takes up plasma. New blood vessels begin growing into the graft within 36 hours (capillary inosculcation) and link up with existing vasculature in the graft, effectively 'plugging' the graft into the host circulatory system³⁵.

Cells of the graft secrete matrix proteins and remodeling enzymes, such as matrix metalloproteases that reorganize the ECM, connecting the graft to the surrounding skin. Re-epithelialisation of the wound edge rapidly occurs through the migration and proliferation of activated keratinocytes originating from both graft and surrounding host tissue. The remodeling of the matricellular proteins in the wound bed begins after approximately four weeks and can continue for years after injury. The maximum collagen deposition occurs three weeks into the healing process²⁸. Following this, a dynamic equilibrium of collagen remodeling is maintained³³. The wound never attains the strength of uninjured skin and reaches its maximum strength (80 %) in twelve weeks.

In the skin, repair and regeneration can be viewed as exclusive processes in response to a wound stimulus⁶. Regeneration is recreation of tissue which is equivalent to the uninjured tissue, whereas the reparative wound closure process, outlined above, results in morphologically different, mechanically and functionally deficient tissue (scar tissue). Following full thickness skin injury collagen

fibers are orientated in parallel bundles rather than in the basket weave arrangement of uninjured skin³⁶. In post fetal skin only wounds involving the epidermis are capable of regenerative healing. Authors have proposed several theories as to why adult tissue fails to regenerate including increased contractile myofibroblasts^{37,38}, decreasing levels of hyaluronan³⁹⁻⁴¹ and lack of blastema formation due to interference from scar tissue⁴².

ASSESSING AND TREATING CUTANEOUS INJURY

In order to apply the correct treatment to a defect it is important to assess the depth of the damage, critically it is this feature that determines the quality and appearance of the resulting scar²⁸. Cutaneous wounds can be classified into four categories based on this (Figure 66-2). Epidermal injuries, characterized by erythema and minor pain, do not require surgical intervention and heal rapidly through the epidermal regeneration process. Partial thickness injuries involve the epidermis and only the most superficial layers of the dermis (previously 1st degree). These wounds are characterized by epidermal blistering and severe pain. In these wounds re-epithelialization occurs from the wound margin through the migration and proliferation of activated keratinocytes. These originate from either the remaining portions of hair follicles and sweat glands in the partially injured dermis or from the basal epidermal layer of surrounding viable tissue. Intermediate thickness injuries involve damage to the epidermis and varying depths of dermis and can be described as 'shallow' or 'deep dermal' (2nd degree) and heal in a similar way to partial thickness injuries where the extent of dermal destruction largely determines the wound healing time. These injuries often result in prominent scarring due to the extent fibroblast necrosis and matrix destruction. Full thickness injuries involve damage to the epithelium and the entire dermis can extend into the subcutaneous adipose tissue (3rd degree). These injuries are highly susceptible to infection due to the break down of desiccated tissue. Full thickness injuries are characterized by complete loss of epithelial regenerative structures in the dermis and as such heal solely by contraction with epithelialization from the edge of the wound. As such, wounds with this depth of damage as small as 4 cm in diameter will not heal effectively without surgical intervention⁴³. In addition to depth and surface area, another critical factor in the restoration of normal function and appearance of injured skin is wound closure time. The incidence of extensive, pronounced hypertrophic scars increases in proportion with the length of time to wound closure. This was demonstrated in a pediatric burn study where wounds that took longer than three weeks to heal resulted in higher proportions of hypertrophic scarring⁴⁴.

The current 'gold standard' treatment for wounds too extensive or deep to heal satisfactorily on their own

is split-thickness autografts⁴⁵. This technique involves the harvest of epidermis and superficial dermis from an undamaged site on the patient's body and grafting into the wound site. Although undoubtedly a success in terms of decreasing mortality rates amongst heavily burned patients⁴⁶ they are rarely used in the treatment of chronic injury due, in part, to the potential for creating another chronic injury at the graft harvest site. A further concern for clinicians is the scarcity of donor sites and the problems of creating permanent scars through over-harvest of graft tissue in patients with large areas of skin loss. Any graft site has the potential to become a very painful wound itself and many go on to form a minor scar with altered pigmentation when healed²⁸. Allografts and xenografts may be used to provide coverage but there are issues such as graft rejection and disease transmission as well as cultural and ethical considerations, surrounding their use⁴⁷.

NECESSITY AND PRINCIPLES OF SKIN TISSUE ENGINEERING

The development of skin substitutes arose from a clinical need to replace or vastly improve results from these current limited approaches. In the conventional treatment of acute injuries, efforts have been made to expand the area that a split thickness skin graft can cover through meshing, however this technique is problematic. Meshing involves the uniform perforation of a skin graft, allowing stretching over larger wound areas. This practice is a success in terms of decreasing mortality rates among the severely burned⁴⁸, but functional and aesthetic outcomes are poor and not comparable to split thickness autografts⁴⁸. This poor performance can be attributed to added contraction of the graft due to lack of dermis in the graft interstices⁴⁸. In addition to this contraction, epithelialization across the interstices is also slow, often resulting in a reptile-like scaly appearance to the skin. Conventional chronic wound treatments such as repeated debridement, saline-moistened gauze and pressure-relieving orthotics often fail to heal many chronic wounds. It is this group of unresponsive wounds that skin substitutes could have the biggest impact upon in reducing ongoing treatment and increasing patient quality of life.

The search for the ideal skin substitute has led to the development of numerous types of products. For these, as with all tissue engineered products, to be successful there are three main considerations that must be taken into account;

- i) Safety – Any cell culture material carries the risk of infection when implanted. Xenogeneic and allogeneic material must be carefully screened prior to use.
- ii) Clinical efficacy – It is also essential that a substitute can be demonstrated to effectively heal wounds and to not be rejected by the immune system.
- iii) Ease of use – A substitute must be easy to use in order to achieve widespread use⁴⁵.

One additional consideration that could be added to this list is cost effectiveness. A low cost to high benefit ratio is a must for a product to achieve truly widespread use. Indeed, one of the main problems with current tissue engineered skin is the high cost for little, if any, added patient benefit over other less costly alternatives.

The subsequent review of current skin substitutes is organized into categories based upon the layer of skin they are designed to regenerate. Where clinical evidence is available, an evidence based approach is used to appraise substitute healing. In some cases little clinical evidence is available and as such critical review of these products is difficult. In these cases, as informed a comment as possible is made by the authors in relation to the effectiveness of the substitute design.

EPIDERMAL SUBSTITUTES (TABLE 66-2)

Modern tissue engineered epidermal substitutes have developed from work which established that suspensions of epithelial cells could be isolated from the skin by trypsinization^{6,49,50}. Subsequently, problems with keratinocyte *in vitro* expansion were overcome by Rheinwald and Green who demonstrated *in vitro* expansion of keratinocytes, achieving an expansion factor of over 10,000 within three to four weeks culture⁵¹. From this cultured epithelial autografts (CEAs), composed of a confluent sheet of culture expanded keratinocytes obtained from a small sample of the patient's own skin were developed. Cultured epithelial autografts can be considered the earliest example of tissue engineered epidermis^{6,18}. The development of a moderately high level of epidermal maturity *in vitro* has been achieved with few difficulties⁵¹⁻⁵³.

Amongst the first clinical application of this technique was by O'Connor and co-workers in 1981 (LOE-5) to treat major burn injuries⁵⁴. In this preliminary case the authors reported that the future use of CEAs was feasible but that infection resulting in graft loss was likely to be a problem⁵⁴. Since then, CEAs have most widely been used in the treatment of major burns⁵⁵ with reported results varying from 'potentially lifesaving'^{56,57} to 'no demonstrable effect on outcome of extensively burned patients'⁵⁸. CEAs are commercially available as Epicel™, EPIBASE™ and Epidex™. Epicel™ and EPIBASE™ contain keratinocytes from the interfollicular skin on a petrolatum gauze backing. Epidex™ contains keratinocytes extracted from the outer root sheath of the hair follicle on a silicone membrane.

There exists little level 1 evidence investigating CEA use in the treatment of major burns. However, in a comprehensive review Wood and co-workers classify the limited level of evidence of studies investigating CEA use⁵⁵. The majority of identified reports were case studies (LOE-5) or case series (LOE-4) with highly variable results making the effectiveness of CEA application difficult to assess⁵⁵. Wood and co-workers do however identify seven main issues with CEA use that are consistently raised by clinicians⁵⁵.

These are 1) time taken to culture cells for clinical use 2) preparation and provision of an appropriate wound bed 3) vulnerability to infection 4) difficulty in assessing take 5) long-term fragility 6) cost of treatment and 7) quality of outcome. Some of these problems, such as vulnerability to infection, quality of outcome and long-term fragility are common amongst all current skin substitutes and tissue engineered products as a whole.

Initially, one of the main problems encountered when using autologous CEAs was the culture period of five weeks required to expand cell samples⁵⁴. Through optimization of the process this culture time was reduced to three weeks in the early 1990's⁵⁹. This delay remains detrimental to the successful treatment of patients, especially in burns patients where a stop-gap alternative is required while the substitute is constructed⁵⁵. This culture time also decreases the proportion of viable cells within lower epidermal portions of CEA sheets due to insufficient nutrient diffusion²⁸. As it is these basal cells that are the attachment site for the graft, it is essential that these cells are viable if the graft is to 'take' to the wound. Achieving the correct timing to enhance success is difficult, enough cells to partially stratify and to make handling easier is desirable but too many cells isolates basal cells from the nutrient medium, resulting in non-viable cells in the dividing, attachment cell layer. Additionally, partial stratification of CEAs *in vitro* has been investigated but has been reported to be fragile, with grafted substitutes prone to blistering owing to poor basement membrane formation⁵⁵. These issues are probable reasons behind reported unpredictable clinical outcomes with CEA use²⁸.

In an effort to reduce both culture time and improve total cell viability, some researchers endeavored to devise systems to deliver sub-confluent autologous cells to the healing wound. This resulted in the development of two main techniques, the culturing/attachment of cells *in vitro* to a carrier membrane (e.g. Laserskin™ and Myskin™), or the creation of a cell suspension which is then delivered as a spray (CellSpray™).

Of these two methods, keratinocyte suspension spray is perhaps the most intriguing due to the exceptional ease and speed of application this method could confer. The first reported clinical use of this delivery method was reported by Hunyadi and co-workers⁶⁰. In this study burn wounds and chronic leg ulcers were healed completely with the application of non-cultured keratinocyte suspensions with fibrin matrix⁶⁰. CellSpray™, a commercially available non-cultured keratinocyte suspension kit, was developed in 1994 in Australia by Fiona Wood⁶¹. In a small case series Zweifel and co-workers report the use of cell spray alone and in conjunction with split thickness autologous grafts to treat deep dermal to full thickness burns⁶². Used alone, CellSpray™ was reported to show promising results in terms of accelerated wound closure and scar quality⁶². When used in conjunction with split thickness grafts it was reported that full thickness wound healing would have

TABLE 66-2—Epidermal Substitutes

Product	Description	Application	Clinical Efficacy	LOE	Strength of Recommendation	Refs
Epicel™ and Epidex™	Confluent autologous keratinocytes from skin on petrolatum gauze backing Confluent autologous keratinocytes from hair follicles outer root sheath on silicone membrane	FTB, PTB, DU, VU	-Variable outcomes dependent on wound bed preparation and culture time. -Technically difficult to apply. -Long culture time prior to use.	2a, 2a, 2a, 1, 2b, 2a	B2	55–57, 167–169
Laserskin™ (vivoderm™)	Subconfluent autologous keratinocytes seeded on esterified laser-perforated hyaluronic acid matrix	FTB, PTB, DU, VU, Tattoo removal	-Heals diabetic foot ulcers and tattoo removal wounds more effectively than conventional treatment in low evidence studies.	4, 4, 4, 1, 4	B2	65–67, 69, 170
Myskin™	Subconfluent autologous keratinocytes seeded on specially treated silicone sheet	PTB, DU, VU	-Requires further clinical trials. -Healed diabetic ulcers that were unresponsive to conventional treatment with 6–17 applications (LOE-4). -Shows potential for treatment of burns	2b, 4, 4	C	70, 171, 71
CellSpray™	Preconfluent autologous keratinocytes delivered into a suspension for spray	PTB, DU, VU	-Accelerates wound closure most effectively in conjunction with split thickness autografts. -Possibility of fragile epidermis due to poorly formed BM	4, 4, 2a	C	61, 172, 173
Suprathel	Acellular co-polymer based on DL-Lactide (70%) but also containing trimethylenecarbonate and ε-caprolactone.	PTB/W, PTD	-Excellent flexibility and adherence to wound bed maintained throughout healing process. -Removal by polymer degradation leaves tissue intact. - Superior pain relief to conventional dressings.	2a, 2b, 2b, 3	B2	81–83, 85
Cryoskin™	Cryopreserved (viable cells) confluent allogenic keratinocytes delivered on a gel-like proprietary chemical surface	Pending Approval	-Treat burn injuries with no adverse immune reaction observed. -Similar results reported with fresh and cryopreserved keratinocytes. -Low cost alternative to other skin substitutes.	4	C	174

Strength of recommendations, (A) There is excellent evidence to support the use of the substitute. (B1) There is good evidence to support the use of the substitute. (B2) There is moderate evidence to support the use of the substitute. (C) There is poor evidence to support the use of the substitute. (D) There is fair evidence to support the rejection of the use of the substitute. (E) There is good evidence to support the rejection of the use of the substitute.

DU, Diabetic Ulcer; VU, Venous Ulcer; FTB/W, Full thickness burn/wound; PTB/W, Partial thickness burn/wound.

been substantially longer without CellSpray™ application⁶². The ease of use of this technique and the reduction in time the patient must spend in prone position were also positives commented upon by the authors⁶². Similar results are reported in a retrospective review of patients treated with CellSpray™ between 1992 and 2002 in Western Australia⁶¹. In comparison to patients receiving CEA sheets CellSpray™ patients stayed in hospital less time and showed less infection⁶¹. The author also comments that in her clinical experience, scar quality is improved in terms of color and contour with the use of CEA suspension⁶¹, although this opinion could be said to not be completely objective. Although easy to apply, authors have raised concerns when using CellSpray™ that healing rate may be inhibited by the need to form the stratified epidermis from unorganized cells at different stages along the terminal keratinocyte differentiation pathway⁶¹. In a similar way to CEAs, the epidermis that is formed may be fragile and vulnerable to mechanical stress due to a poorly formed basement membrane^{63,64}.

Naturally occurring extra cellular molecules in the epidermis often require modification before they are suitable for supporting keratinocyte growth and transport due to poor mechanical properties. One example, Laserskin™, utilizes a three-dimensional heavily cross-linked hyaluronan-based matrix which is perforated by laser and contains pre-confluent autologous keratinocytes⁶⁵⁻⁶⁷. Hyaluronan is a glucosaminoglycan (GAG) found ubiquitously in ECM throughout the body and known to be involved in cell proliferation, migration and angiogenesis⁶⁸. Initial success has been observed with this material in a pilot study involving 14 patients with diabetic foot ulcers that resisted conventional treatment for at least six months⁶⁷. Laserskin™ application resulted in 11 of the 14 wounds closing within a mean time period of 41 ± 18 days⁶⁷. In another study investigating Laserskin™ use in patients that have undergone tattoo removal, the substitute was seen to be advantageous as a single application for a 2-week period was sufficient during healing⁶⁹.

Myskin™ makes use of a treated silicone sheet to transfer subconfluent autologous keratinocytes to the wound bed. The potential of Myskin™ to be a successful tool in the treatment of chronic diabetic neuropathic ulcers has been demonstrated in a series of clinical trials. The ulcers in the trials had previously been unresponsive to conventional therapy. But Following 6 to 17 applications of Myskin™, complete healing was achieved in 67 % of ulcers, whilst a reduction in size was observed in one of those remaining. In this case, only one of the ulcers failed to respond after 24 applications of Myskin™⁷⁰. No recurrences in the healed ulcers were observed after six months follow up. Myskin™ has also demonstrated potential in the treatment of acute burn injuries where application of the substitute healed two injuries on two patients successfully⁷¹.

Whilst the transfer of sub-confluent autologous cells is advantageous in terms of time to treatment in order for a similar number of cells to be delivered larger initial

samples are needed. In addition to this, there is a consistent problem with graft fragility due to a lack of epidermal stratification and poor basement membrane assembly and organisation. It would appear that for these delivery methods to achieve their potential a way to enhance the grafted cells characteristics must be employed. This could be through the incorporation of growth factors or cytokines into carrier matrices or suspension media, or alternatively through genetic modification of cells. Future developments and current advances will be discussed in greater detail later within this review.

An alternative to transferring sub-confluent keratinocytes is to utilize the structure of formed epidermis by transferring fresh or cryopreserved split-thickness donor skin. Although not strictly tissue engineered skin this source of graft skin is worthy of note. Recently, techniques have been developed for the large scale production of high quality cryopreserved epithelium⁷²⁻⁷⁴. In a comparative study, cryopreserved keratinocytes were demonstrated to treat wounds faster and more efficiently than conventional hydrocolloid dressings⁷⁵. Additionally, comparable results between fresh and cryopreserved keratinocytes have been reported, suggesting that cryopreservation and storage does not damage the wound-healing potential of the cells⁷⁵. Cryoskin™ (previously CryoCeal™) consists of several layers of keratinocytes on an inert nylon gauze, obtained from heart-beating multi-organ donors and stored in cryopreservation medium⁷⁶. The use of Cryoskin™ in combination with meshed autologous grafts for the treatment of burn injuries was investigated in a trial involving 117 patients⁷⁷. The study reported that no adverse immune reaction to the allogeneic material was observed⁷⁷. The use of cryopreserved keratinocytes in the treatment of chronic leg ulcers has been shown to decrease the time to complete wound closure in several independent studies^{76,78-80}. Authors additionally mention that the use of cryopreserved keratinocytes has the advantage of being simple and safe to use whilst decreasing patient discomfort for a lower cost than other skin substitutes^{76,79}.

Of note is the recent development of the acellular epidermal substitute Suprathel. Although the synthetic scaffold may be considered a wound dressing it has shown promise in treating partial thickness burn injuries and split thickness skin graft donor sites^{81,82}. The substitute is composed of a copolymer which is >70% DL-lactide but also contains trimethylene carbonate and e-caprolactone and is designed to mimic the properties of natural ECM. The production of Suprathel from monomer polymerization by a melt procedure, dissolution in organic solvents, phase inversion and freeze drying results in a highly porous (80 %) membrane, with pore sizes ranging from 2-50 µm⁸². The material itself has several interesting properties that make it ideal as an epidermal substitute. Firstly, it has high elasticity and flexibility at body temperature, allowing the substitute to closely fit to the wound bed. Secondly, it is permeable to water preventing the build up

of fluid. Thirdly, it has been found to be transparent when applied to the wound, allowing visual inspection. Perhaps most innovative is the process of detachment from the healed wound through polymer molecular weight decrease, leaving the fully epithelialized tissue intact.⁸²

Suprathel was approved as a CE class III medical device in 2004 based on the results of a bicentric, randomized, non-blinded clinical study⁸³. In this study, Suprathel was compared intra-individually with paraffin guaze and Omiderm for use in the treatment of split thickness donor sites and partial thickness burns respectively. For the first indication, a major concern is the reduction in pain following treatment. Using the Visual Pain Analog Scale (VAS) the average cumulative pain score for 10 days following application was 9 for Suprathel and 21.7 for paraffin⁸³. The authors report that due to the high significance of the results the study was discontinued after 20 patients⁸³. In comparison with Omiderm for the treatment of partial thickness burns using the VAS scale 19 patients reported higher pain scores for Omiderm, three reported the same levels of pain for both dressings and two reported higher pain for Suprathel treated areas. No significant difference in healing time was reported between Omiderm and Suprathel treated wounds⁸³. Although a significantly better VAS score was reported for Suprathel, the non-blind nature of this trial could have affected the results⁸³. Omiderm has cheaper material costs than Suprathel, however, further studies should be conducted to confirm the significant pain reduction in wounds treated with Suprathel. Additionally, Suprathel is reported to maintain plasticity throughout the healing process, whereas Omiderm has been shown to form a crust when in contact with wound exudates⁸⁴. Suprathel should then be considered for areas that require added flexibility, such as the hands, this is supported by the experiences of Uhlig and co-workers in a single centre study involving 109 patients⁸⁵. In such cases, the added cost of this material may be considered to be worthwhile.

DERMAL SUBSTITUTES (TABLE 66-3)

The dermis provides the mechanical strength to the skin and structural support to the epidermal barrier. Many of the problems encountered upon application of epidermal substitute – e.g. contraction, fragility, poor take – can be exacerbated by the absence of a suitable dermal layer⁸⁶. One study reported that only 15 % of cases resulted in successful ‘take’ of grafts on unprepared chronic granulation tissue²¹. Since a speedy wound closure is of the high importance, it is desirable to construct a functional, well vascularized dermis as quickly as possible. This dermis provides not only mechanical support to the overlying epidermis but also to supply the avascular epidermis with nutrients. To accomplish this both acellular scaffolds (constructed to allow rapid host cell invasion from the surrounding viable tissue) and cellular scaffolds (replacing damaged or dead tissue directly with viable cells) have been devised.

The vast majority of these porous matrix materials are designed to imitate natural extra cellular matrix (ECM). When transplanted into the patient this matrix is intended to allow rapid cell proliferation and migration, rather than the cells first having to construct their own matrix. A good scaffold material should be strong but flexible, degrade at a rate that is equal to construction of replacement matrix by cells, contain adequate numbers of cell attachment sites and allow rapid cell migration and proliferation.

In designing a scaffold for engineering dermis, emulating the properties of natural matrix may be beneficial. However, the goal of a dermal substitute is accelerated neotissuegenesis, through a process that need not exactly follow that of development or the normal wound healing program. Therefore it may not be necessary or optimal for a successful skin substitute to mimic natural matrix exactly. Rather the manipulation of natural or artificial materials to construct optimal scaffold features could be advantageous. Many products utilize processed natural dermal matrices from various xenogeneic and allogeneic sources. The idea is that a decellularised matrix should retain the properties and matrix bound bioactive molecules present in the natural dermis. This should create a favourable environment for rapid cell migration and proliferation within the substitute. However, mature matrix tissue like this once processed with harsh de-cellularisation techniques to reduce immunogenicity often does not possess the fragile highly interconnected macro- or micro-pore structures needed to allow quick and uniform cell population. Furthermore, useful growth factors bound to the matrix are likely to be denatured or lost during washing. Conversely, mild procedures often fail to completely remove cell fragments, leading to immune reaction. Other substitutes utilize re-organized biomaterials from various sources with collagen the most common choice, perhaps due to its strength, availability and natural prevalence. Alternatively synthetic materials are common either as an additional component to aid stability to the biological component or as the main scaffold material themselves.

At least five of the currently available commercial dermal substitutes are constructed, in part, from xenogeneic material. More specifically these xenogeneic components consist of dermal matrix proteins from bovine and porcine sources. These proteins bear high structural similarity to their human equivalents, providing a cheaper and more easily extracted alternative to their human equivalent. Further to this, their structural homology means that cell adhesion sites and motifs are conserved or closely resemble those seen in human dermal matrix. Due to graft rejection and disease transmission issues xenogeneic substitutes do not contain xenogeneic cellular material.

Decellularized porcine small intestinal submucosa is one material that has been employed in the development of the commercially available substitutes OaSis™ and FortaFlex™. FortaFlex™ is intended to provide a template that can be remodeled by invading cells but has been the

TABLE 66-3—Dermal Substitutes

Product	Description	Application	Clinical Efficacy	LOE	Strength of Recommendation	Refs
Dermagraft™	Cryopreserved (viable cells) allogeneic fibroblast-derived dermal matrix	DU, VU, FTB/W, PTB/W,	-Take rate is inferior in patients treated in conjunction with autograft (LOE-4). -DFU treated with more Dermagraft applied more often heal quicker. -Performance variable – linked to ratio of viable fibroblasts after cryopreservation.	3, 1, 4, 3, 4, 1	B2	122–124, 47, 125, 175
Transcyte™	Similar to Dermagraft, but with a silicone membrane as temporary epidermal barrier	FTW/B, PTW/B,	-More effective than conventional treatment. -Reepithelialization quicker when using TransCyte over Biobrane in burn injuries (LOE-5)	3, 4, 3, 1	B2	47, 130, 132, 176
Alloderm™	Acellular (lyophilized) allogeneic dermis	FTW/B, PTW/B	-Results dependent on technical ability of clinician applying substitute. -Allows use of ultra-thin thickness autograft	3, 4, 4, 4	C	118–120, 177
Oasis™	Acellular porcine small intestine submucosa	FTW/B, PTW/B, VU, DU	-Reported to treat venous/arterial ulcers more effectively than Hyaloskin (LOE-4) -Accelerated healing of graft donor sites and decreased patient pain.	4, 2a, 2a, 3, 4, 4	B2	88–93
EZ-Derm™	Aldehyde crosslinked porcine dermal collagen	FTW/B, PTW/B	-Good short term capability (3 days) in the treatment of burns. -Meshed substitute leaves imprint and should not be used for facial burns.	4, 5, 4, 5	C	94, 96–98
ICX-PRO™	Active allogeneic human fibroblasts in a fibrin-based gel matrix	DU, VU, FTB/W	-Currently in Phase II clinical trials.	5	C	140
Biobrane™	Porcine collagen chemically bound to silicone/nylon membrane	FTW/B, PTB/W	-Widely utilized for the treatment of superficial and partial thickness burns, in particular those involving joints, large surface area and hands. -Has been reported to leave imprint when meshed.	3, 4, 5, 4, 5, 4, 5, 5, 5, 5, 5, 4, 4,	B2	95, 100, 102–113
Integra™	Acellular temporary silicone epidermal substitute over dermal scaffold made of bovine collagen and chondroitin-6-sulphate	FTB/W, PTB/W	-Most widely utilized dermal replacement for extensively burned patients. Also found application in chronic wounds. -Prone to infection and requires slow two stage procedure and autograft. -Good aesthetic and functional outcomes when used properly.	4, 4, 5, 5, 5, 5, 5	B1	28, 178– 180, 134, 137–139
Matriderm™	Acellular fibroblasts made with bovine collagen types I, III, V and elastin	FTB/W, PTB/W	-Effective take with one step procedure. -Effective particularly on hand burns, where elasticity of matrix is benefit.	3, 4, 4, 5, 5	B2	114–117, 181
ICX-SKN™	Allogeneic fibroblasts set in a natural human collagen matrix	Phase II trial pending	-Evidence that ICX-SKN is safe for human use.	5	C	141

DU, Diabetic Ulcer; VU, Venous Ulcer; FTB/W, Full thickness burn/wound; PTB/W, Partial thickness burn/wound.

subject of few clinical trials⁸⁷. Likewise, although the OaSis™ substitute was approved by the FDA in 2000 for use in the treatment of chronic ulcers and burns only a small number of articles have been published into the clinical efficacy of the substitute⁸⁸⁻⁹³. Within these studies, OaSis™ has been mainly utilized for the treatment of chronic ulcers, where it has shown some success.

In a randomized clinical trial for the treatment of venous leg ulcers weekly application of OaSis™ led to healing in 55 % of patients⁹². Similar healing potential was reported by a small multicenter trial comparing OaSis™ and Regranex Gel in the treatment diabetic ulcers⁸⁹. Although this trial was too small to prove statistical significance, the healing of OaSis™ treated wounds was as at least as effective as Regranex Gel after 12 weeks treatment⁸⁹. OaSis™ has also been reported to be superior to another substitute, Hyaloskin™, in the treatment of mixed arterial/venous ulcers⁹⁰. In this study, OaSis™ also was reported to be advantageous in terms of pain relief, patient comfort and time (for dressing changes)⁹⁰. In another application, OaSis™ was investigated as a dressing for split-thickness graft donor sites in 131 patients. Accelerated healing was observed with all but two of the wounds healing in one to three weeks and patients reporting decreased pain, that the authors attribute to nerve-end coverage by the matrix⁹¹. Larger double-blinded randomised clinical trials are needed to prove that the use of this xenogeneic material is an effective alternative treatment.

Instead of utilizing intact matrices several other substitutes employ reconstituted xenogeneic matricellular proteins in some form. These have found more widespread clinical application, with the most prominent of these being EZ-Derm™, Biobrane™ and Matriderm™. EZ-Derm™ is composed of an aldehyde-crosslinked porcine dermal collagen. Aldehyde-treatment in this way decreases the antigenicity of the substitute whilst enhancing its' structural integrity⁹⁴. Biobrane™ is porcine collagen which has been chemically bound to a silicone/nylon membrane first developed by Woodruff in 1979⁹⁵. Matriderm™ is a scaffold composed of bovine collagens types I, III and V, along with elastin.

The efficacy of the similar, porcine collagen based substitutes, EZ-DERM™ and Biobrane™ was compared in a retrospective review of 52 burns patients⁹⁴. The two substitutes both decreased exudative protein loss, protected underlying vessels and nerves (decreasing pain) and promoted the maturation of granulation tissue for autografting to similar level⁹⁴. The authors noted that Biobrane™ adhered to the wound bed with greater success and was more suited to longer term grafting (up to 10 days) in comparison to the shorter term capability of EZ-DERM™ (3 days), which does not incorporate into the wound and must be removed⁹⁴.

The use of these porcine collagen scaffolds has been linked to mesh imprinting of healed wounds if left on the wound for extended periods. For example, meshed EZ-DERM™ in the treatment of facial burns has reportedly

led to scarring⁹⁶. Similarly, the use of Biobrane™ has also led to scarring corresponding to the pores in the substitute⁹⁷. However, authors have since reported unmeshed EZ-DERM™ substitutes do not leave an imprint on healing even if left on the wound for up to 20 days⁹⁸.

The efficacy of Biobrane against more conventional dressings has also been investigated in a randomized prospective study comparing Biobrane and Duoderm hydrocolloid dressing for the treatment of intermediate burns in pediatric patients. Biobrane was found to show no therapeutic advantage despite significantly higher treatment costs⁹⁹. Having said this, a small randomized trial involving second degree pediatric burns showed that Biobrane performed significantly better than topical 1% silver sulfadiazine. The authors report that Biobrane reduces hospital stay, pain, the amount of pain relief medication needed and wound healing time significantly over the conventional treatment¹⁰⁰. These and other studies are good examples of how in some cases although skin substitutes are superior to topical treatments, their performance may not be significantly better than simpler, cheaper dressings¹⁰¹.

Despite reports of imprinting and comparable performance to cheaper alternatives, Biobrane™ remains a widely utilized substitute in treatment of superficial and moderate depth partial thickness burns^{100,102-105}. In particular it has found a niche in the treatment of burns with a large surface area¹⁰⁶, involving joints¹⁰⁷ and the hands^{108,109} due to the flexibility it confers to the healed wound. For these applications, it has again been shown to be effective in the reduction of pain and healing time in comparison to conventional treatment¹¹⁰⁻¹¹³.

Matriderm™, which utilizes bovine collagens coated with α -elastin hydrolysate, was developed as a one-stage alternative to other two-stage substitutes for application in the treatment of burns. In a one-stage process an epidermal layer, either epidermal substitute or graft, is directly applied onto the dermal replacement or graft. This one-stage approach is facilitated by the thinness of Matriderm™ and the diffusion of nutrients through it. A one-stage process allows speedier coverage of the wound bed but has not been previously favored due to poor take on the low quality dermis (or lack thereof) of the grafted dermal scaffold¹¹⁴. However, it has been shown that even when using a one step process, the take of Matriderm™ is unaffected in clinical trials (overall take rate 97 %)^{114,115}. Matriderm™ has particularly shown promise in the treatment of burns to the hands and areas requiring flexibility^{114,116,117}. Restoring function after injury is of key importance in hand injuries for the restitution of a quality of life. The elastin present in the Matriderm™ matrix may provide the flexibility needed to return freedom of movement to the healed wounds¹¹⁴.

In parallel to the development of these xenogeneic substitutes, several similar substitutes have been constructed using allogenic material, and, allogeneic plus synthetic material. AlloDerm™ and Repliform™ are both

based on acellular allogeneic dermis, although AlloDerm™ is lyophilized whilst Repliform™ is not⁵. Cymetra™ also contains acellular human dermal matrix, obtained from cadaver skin and processed into micronized particles⁵.

In a comparative study, Wainwright investigated AlloDerm™ in combination with meshed autograft and meshed autograft alone, for the treatment of full thickness wounds in two patients¹¹⁸. Qualitative assessment of elasticity and cosmesis favoured AlloDerm™ autograft combination¹¹⁸. This small study was expanded on in a multicentre study involving 67 patients and ten centres¹¹⁹. The results from this study are difficult to interpret. The authors state that the failure of centres to follow the approved methodology for the use of AlloDerm™ resulted in poor results¹¹⁹. However, the authors do state that when using AlloDerm™ it is possible to use a thinner autograft, which is beneficial for the healing of donor sites¹¹⁹. Another study comparing AlloDerm™ in combination with a thin autograft and thicker autograft alone to treat burns to the hands and feet was reported by Lattari and co-workers¹²⁰. Wounds were assessed for cosmetic appearance and functionality, with AlloDerm™ wounds and autograft-only wounds highly similar to each other as assessed by a blinded observer using the Vancouver Scar Scoring system¹²⁰.

Two of the most widely studied dermal substitutes, Dermagraft™ and TransCyt™, have similar compositions and contain a cellular component. They both include cryopreserved (viable) allogeneic fibroblasts grown in a polyglactin 910 or polyglycolic acid bioabsorbable mesh. This material allows the fibroblasts to deposit extra cellular proteins and negates the use of exogenous collagens¹²¹.

Dermagraft™ has been investigated for use in the treatment of both acute and chronic injuries. In a clinical trial involving 17 full thickness burns patients Dermagraft™ in conjunction with a split thickness meshed autograft was compared to meshed autograft alone¹²². However, the findings of this study indicated that take rate was inferior in patients treated with both Dermagraft™ and an autograft, in contrast to other dermal substitutes¹²². This indicates that perhaps other materials should be considered for this indication rather than Dermagraft™.

However, Dermagraft™ has found application for the treatment of chronic diabetic foot ulcers. In a controlled trial involving 50 patients it was reported that wounds healed faster and more completely when a greater amount of Dermagraft™ was applied and when it was applied more frequently¹²³. This result was supported by a larger randomized, controlled series, involving 281 patients with diabetic foot ulcers¹²⁴. A total of 50.8 percent of the dermal replacement-treated group exhibited complete wound healing at 12 weeks compared to 31.7 % in the control group¹²⁴. However, Dermagraft™ use in for this application is not without issue, with the main problem being inter-graft variation in levels of cell viability. The performance of the substitute for healing chronic wounds has been shown to be dependent on the viability of the fibroblasts within

it¹²⁵. If viability is severely decreased, for example through the cryopreservation process during manufacture, then the substitute fails to heal effectively¹²⁵. This data does suggest that cytokine, growth factor and ECM secretion could be responsible for the healing properties observed, although this is not the way the product was initially designed to work^{125,126}.

TransCyt™ is designed as a temporary biosynthetic covering and is composed of a semi-permeable silicone membrane and neonatal fibroblasts cultured on a porcine collagen coated nylon mesh¹²⁷. It has been used as a temporary covering for wounds prior to autografting, or in wounds that do not require autograft^{47,127}. TransCyt™ has been shown to out perform conventional treatments (in conjunction with silver sulfadiazine and topical antibiotics)¹²⁷⁻¹³⁰. The use of TransCyt™ in these cases resulted in a more rapid healing time, lower amounts of infection¹³⁰, better wound closure and scar severity and less dressing changes^{128,129}. The authors of these studies report improved wound management including decreased pain and length of stay¹³¹. In a larger study (n = 110), burns patients who treated with dermabrasion and TransCyt™ were 6 % less likely to require autograft¹³². In another randomized comparative trial 33 burns patients (58 wounds) were treated with Silvazine (silver sulphadiazine cream with 0.2 % chlorhexidine), Biobrane™ or TransCyt™. Mean reepithelialization time when using TransCyt was shorter (7.5 days) compared to either Biobrane™ or Silvazine (9.5 days and 11.2 days respectively) ($p < 0.001$). Wounds treated with either of the skin substitutes tested in this study required significantly fewer autografts than those treated conventionally (24 % vs. 17 % (Biobrane™) and 5 % (TransCyt™)). However, the authors neglect to describe the randomization process or how the assessment of epithelialization was made, possibly compromising the results.

Integra™ is amongst the most widely used synthetic dermal substitutes and was first described by Yannas and Burke in 1980¹³³. It is composed of bovine type I collagen and shark chondroitin-6-sulfate with a temporary silicone membrane to restore epidermal barrier function. Integra™ is normally applied to the freshly excised wound bed where the collagen component integrates over a three to four month period²⁸. The collagen component of the Integra™ is designed with a pore size (20-120 μm) that promotes autologous cell migration whilst maintaining enough surface area for cell attachment¹³⁴. Once the dermal component is fully integrated (15-20 days) the silicone epidermal portion is removed and a ultra-thin split autograft is applied²⁸. Integra™ has shown success in the treatment of full thickness thermal and non-thermal trauma and chronic ulcers. This material has several advantageous characteristics including long shelf life, straightforward handling, positive aesthetic and functional outcomes and low incidences of contraction and pronounced scarring^{48,135}.

Having said this, the use of Integra™ has a number of negatives including a steep learning curve for clinicians,

closely associated with graft success. Additionally, it is essential when using Integra™ to thoroughly surgically debride the wound bed for the substitute to "take". A further limitation of this substitute design is the need for a second surgical procedure and the eventual use of an autograft, albeit a super thin one. Aside from these technical limitations, there are two additional main problems with Integra™. The first of these is the long re-vascularisation period (10-15 days) required for the neo-dermis and the second is the high reported incidence of infection, although this does appear to decrease with clinical experience¹³⁶.

Efforts have been made to incorporate Integra™ into a single stage graft procedure. A single case study reports the successful combination of Integra™ with a CEA sheet, with little success¹³⁷. An alternative approach that has been investigated is the pre-seeding of Integra™ with either cultured autologous keratinocytes prior to grafting¹³⁸ or freshly isolated cell suspension¹³⁹. Initially this technique seemed promising with successful animal studies showing epithelial coverage after ten days¹³⁸. In a clinical trial an epidermal layer was produced after 3 weeks but quickly deteriorated suggesting that the cells were unable to maintain the required epidermal cell turnover²⁸. Seeding Integra™ with epidermal stem cells could be a possible way to prevent this deterioration.

The limited success of these older skin substitutes has driven the development of the second generation of engineered skin. ICX-PRO™ and ICX-SKN™, both developed by Intercytes, are such substitutes. They, and others, have been designed to build upon the valuable lessons learnt from the likes of Dermagraft™, Apligraf™ and TransCyte™¹⁴⁰. As such they are intended to be the most cost effective and easiest to use substitute available to date. One area in which ICX-PRO™ has succeeded is to decrease its assembly time and has a much shorter manufacturing cycle than other substitutes, taking 1 day to manufacture¹⁴⁰. It is delivered in an easy to use package and can be stored for 21 days in a refrigerator¹⁴⁰. ICX-PRO™ is currently involved in phase III clinical trials¹⁴⁰.

The focus of the ICX-SKN™ substitute has been to generate a collagenous matrix stable enough to withstand the harsh environment of the wound bed¹⁴⁰. It contains neonatal foreskin-derived dermal fibroblasts seeded into autosynthesised collagen and other human plasma proteins, including fibrin and fibronectin¹⁴¹. Effectively this reconstructs the wound bed environment *in vitro*. This process of collagen autosynthesis rather than degradation and reassembly collagen leads to a more robust structure and slower degradation once implanted¹⁴¹. A small clinical trial demonstrated the safety of this substitute and showed re-epithelialization of the wounds¹⁴¹. The exact mechanism of action of ICX-SKN™ in this trial is not known and requires further investigation.

BILAYER SUBSTITUTES (TABLE 66-4)

Bilayer substitutes can be considered the most advanced class of skin substitutes in terms of structural mimicry of

natural skin as they contain both epidermal and dermal layers. Unfortunately this complexity also means that they are the most expensive substitutes on the market and as such must exhibit a significant clinical advantage over their less advanced counterparts; the dermal and epidermal substitutes, to justify utilization. Most bilayer substitutes incorporate an allogeneic cellular component that allows the product to be produced with less delay.

Some products do incorporate autologous cells, PermaDerm™ is one such product and is similar in design to Integra™. Although recently sold to Lonza in 2007 there are currently no clinical trials involving PermaDerm™. Orcel™ and Apligraf™ (Graftskin) are also based on a similar model to each other. Apligraf™ is constructed of human fibroblasts seeded onto a bovine type I collagen scaffold. This fibroblast/collagen mixture then undergoes fibrillogenesis and forms a gel. The collagen fibers condense, mediated by the fibroblasts, resulting in a dense lattice¹²⁶. Keratinocytes are then seeded onto the lattice and allowed to differentiate and form a stratified epidermis with a functional stratum corneum¹²⁶. The cells used in the substitute can be allogeneic, autologous or a combination of the two¹²⁷. Upon application this composition gives Apligraf™ a similar appearance and handling characteristics to that of native skin¹⁴². As with other substitutes containing metabolically active viable cells these products have a shelf-life of just five days at room temperature¹²⁷.

Apligraf™ was originally designed as an organotypic skin substitute but its allogeneic cell component has been reported to be completely removed by one to two months after implantation, although no acute immune rejection is observed^{143,144}. Despite this, the substitute has been shown to exert some healing potential, in effect acting as a biologically active temporary dressing. Apligraf™ achieves this through the delivery of cytokines (Interferon α, Interferon β, Interleukins 1, 6 and 8), growth factors (e.g. platelet-derived growth factor (PDGF) and extra cellular matrix components to the wound bed^{145,146}.

The short life span of allogeneic cellular material in Apligraf™ means that they are unsuitable for the treatment of full thickness wounds, as definitive wound closure cannot be reached. In an effort to increase life span of the substitute autologous cells have been incorporated, either by split thickness skin grafts along side allogeneic cells or as cellular replacements for allogeneic material.

A combination of allogeneic fibroblasts and autologous keratinocytes was investigated in a preliminary clinical trial on six patients with burns or non-healing donor sites¹⁴⁷. Results from this trial were variable with percentage take rates ranging from 0 to 100 %. A positive point was that the technique allowed a 15-20 fold expansion of donor skin in just 4-7 days¹⁴⁷ but negatives associated with autologous cell use apply¹⁴⁸.

In a multicenter, randomized, controlled trial in burn patients, wounds were treated with Apligraf™ in combination with meshed autografts. The wounds treated in this

TABLE 66-4—Bilayer Skin Substitute

Product	Description	Application	Clinical Efficacy	LOE	Strength of Recommendation	Refs
OrCel™	Allogeneic keratinocytes seeded over dermal scaffolds (bovine collagen sponge) containing allogeneic fibroblasts	PTB/W	-Useful tool for quick regeneration of graft donor sites for re-use. -Fragile, quickly deteriorates in wound environment. -Healed burn sites more rapidly than Biobrane-L™.	4, 5	C	182–183
Apligraf™	Human fibroblasts seeded over bovine collagen scaffold. Keratinocytes seeded onto mature matrix.	VU, DU	-Variable take rates reported. -Effective as temporary covering over meshed autografts. -Contraction and deterioration in wound a reported problem. -Found to be more effective than conventional treatment for diabetic ulcers.	5, 4, 5, 4, 4, 5, 4, 2a	C	127, 148, 149, 147, 143, 150, 105, 152
TissueTech™ autograft system	Combination of Hyalograft 3D™ and Laserskin™	FTB/W, PTB/W, VU, DU	-Heal ulcers resistant to conventional treatment. -Similar performance to Dermagraft™ and Apligraf™ -Provide a cost-benefit gain over time in comparison to conventional treatment.	5, 3, 5, 4, 2a, 4, 4, 5	C	66, 156, 154, 153, 156, 184–185
StrataGraft	Second generation substitute providing dermis and fully stratified epidermis composed of viable NIKS cells.	FTB/W, PTB/W	-Comparable performance to cadaver skin graft. -Skin appears healthier and is more adherent to graft when used compared to cadaver skin. -Availability, uniformity and low infection risk benefits.	1	B2	159

DU, Diabetic Ulcer; VU, Venous Ulcer; FTB/W, Full thickness burn/wound; PTB/W, Partial thickness burn/wound.

way healed statistically better than the control (mesh graft alone) at all time points from week one to 24¹⁴⁸. This interesting result warrants further investigation of Apligraf™ for this application. In a case series the effectiveness of Apligraf™ for treating wounds caused by the surgical removal of skin cancers or keratoacanthomas was investigated¹⁴⁹. Apligraf™ application resulted in contraction of wounds by 10–15 %, slightly more than that seen with full thickness grafts¹⁴⁹. This initial clinical experience was extended into a multi-centre trial involving 107 patients in 10 centres¹⁴³. During this larger trial graft persistence was reported as 73 % at 1 week, 53 % at 1 month and 31 % at 1 year^{126,143}. Infection rate was reported at a relatively high 10.5 %¹⁴³.

Currently, Apligraf™ is only licensed for the treatment of venous and diabetic foot ulcers where its application has demonstrated significant advantage over conventional treatment. A comparative trial between Apligraf™ and multilayered compression therapy for this application, involving 233 patients and 15 centres was conducted by Sabolinski and co-workers¹⁵⁰. At six months post-grafting 61 % of Apligraf™ treated wounds were completely healed as apposed to 44 % treated conventionally¹⁵⁰. Apligraf™ treated wounds also exhibited a more rapid median time to complete wound closure of 57 days as apposed to

181 days for conventionally treated wounds^{150,151}. Similar healing potential was reported by Veves and co-workers in the treatment of 208 diabetic ulcers, where 56 % and 38 % of ulcers healed in 12 weeks with Apligraf™ and conventional treatment respectively¹⁵². Despite this, it is still debatable whether the clinical benefits observed in chronic ulcer treatment are large enough to justify widespread use of Apligraf™. At £17 per centimeter squared Apligraf™ is expensive in relation to less developed dermal substitutes, which may be able to deliver similar results.

TissueTech™ autograft system is a combination of the dermal substitute Hyalograft 3D™ and the epidermal substitute Laserskin™. The TissueTech™ system cannot be classified of a true bilayer substitute due to the separate components and the two stage application process. It offers a completely engineered treatment option but could become complicated when used in clinical practice.

In preliminary studies TissueTech™ has proven to be particularly useful for treating ulcers that have resisted healing through conventional techniques^{66,153}. Initial reports in an observational study in the treatment of diabetic foot ulcers of a healing rate of 91 % with a mean healing time of 72.7 ± 48.2 days¹⁵⁴ were supported by a randomized controlled clinical trial where 65 % healing was

observed¹⁵⁵. In an additional, large retrospective clinical review, the TissueTech™ system was assessed for treatment of chronic lower extremity wounds¹⁵⁶. This review featured data on 975 patients (1156 wounds) and concluded that the substitute is a 'safe and effective treatment for chronic wounds, which could even provide a cost-benefit gain over time'¹⁵⁶. In a LOE-1, detailed, retrospective review of the use of TissueTech™ for treating diabetic foot ulcers comprising 401 wounds in 346 patients from 60 centres¹⁵⁷. In this review the authors state that the performance of TissueTech™ reported is similar to that reported by randomized, controlled clinical trials involving established substitutes Dermagraft™¹²⁴ and Apligraf™¹⁵². In terms of healing rates, the authors state that TissueTech™ performs significantly higher than current conventional treatment studies¹⁵⁸.

The Orcell™ construct is composed of a bovine collagen type I sponge seeded with allogeneic neonatal fibroblasts. This sponge is coated with a collagen gel on the upper exterior, serving as a platform for neonatal allogeneic keratinocytes to form a confluent sheet. In a similar way to Apligraf™ due to this product's allogeneic cell component which does not survive in the long term it is thought to exert its effect through the release of cytokines and growth factors.

StrataGraft is a second generation skin substitute providing a dermis and fully stratified epidermis composed of keratinocytes from a genetically stable, pathogen-free, long lived progenitor cell line (Neonatal Immortalized KeratinocyteS, NIKS)¹⁵⁹. The epidermal barrier function of this substitute is reported to be comparable to that of uninjured skin¹⁵⁹. A comparative study between Stratagraft and cadaver allograft in patients undergoing sequential skin reconstruction procedures prior to autograft placement

was the basis of an FDA Investigational New Drug application¹⁵⁹. In a phase I/II multicentre, non-blind, randomized, safety, dose escalation trial 15 patients wound sites received 50 % Stratagraft and 50 % cadaver allograft treatment¹⁵⁹. The total body surface area treated with Stratagraft was increased from 0.5 %, to 1 %, to 1.5 % during the course of the trial. Following wound bed preparation with either treatment, subsequent autograft take and occurrence of infection was measured. The performance of Stratagraft and cadaver skin was not statistically different in terms of autograft 'take' or occurrence of infection¹⁵⁹. However, the Stratagraft treated wounds were deemed to be more adherent and pink in colour than cadaver skin treated wounds¹⁵⁹. This study demonstrates that this viable cell scaffold performs as well as the current standard of care and has obvious advantages such as availability and mass production whilst not disintegrating in the wound bed like first generation scaffolds^{159,160}.

DISCUSSION

Skin substitutes have faced a number of problems in becoming widespread useful clinical tools, including, perhaps most importantly, their high cost and relative underperformance. In addition to this, once in the harsh environment of the wound bed substitutes have often failed to behave as originally intended in the clinical setting. For example, Apligraf™ and OrCell™ break down in the wound and only contribute to healing by secondary intent, rather than as living skin equivalents¹⁴⁰. These almost universal problems can be attributed to nature of substitute design. At the outset of skin engineering researchers designed substitutes (Figure 66-4) that seemingly blindly copied

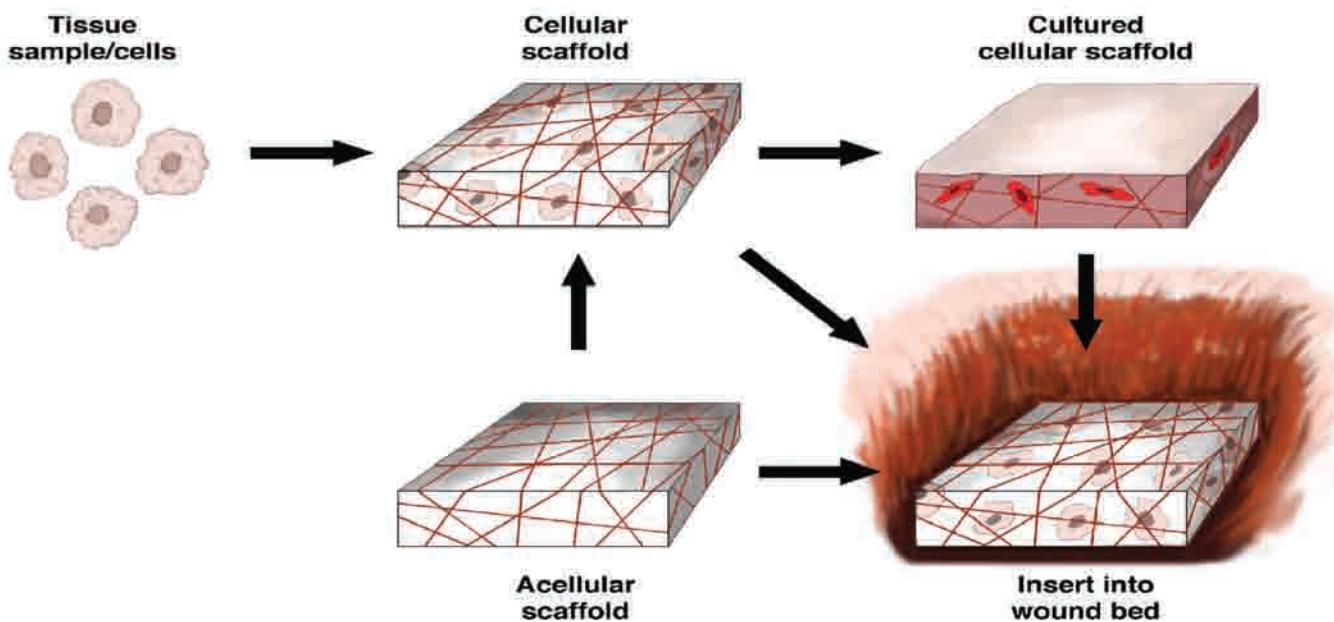


FIGURE 66-4 Simplified diagram comparing different skin engineering strategies.

natural end-point matrix structures or selected healing processes, but disregarding others, rather than designing on the basis of a detailed understanding of what was required. An interesting analogy, made by Kemp in 2006, is that of early aeroplane designers copying the shape of birds wings without really understanding the reason for their shape¹⁴⁰. Quite recently, it was recognized that focusing on the developmental processes that form the natural dermis, ECM and epidermis holds the key to engineer truly effective substitutes with the capacity to regenerate injured skin rather than repair it. An isolated recent example of an attempt to achieve this is the substitute ICX-SKN™. In ICX-SKN™ a collagen matrix is synthesized by fibroblasts seeded into the provided provisional matrix. The authors propose that this results in collagen with a stronger structure than remodeled collagen, similar in structure to that of uninjured collagen¹⁴⁰. This configuration should help to reduce scarring and increase the strength of the wounded area of skin once healed.

The poor cost to benefit ratio of current substitutes is also indicated by the fact that the most utilized substitutes are arguably not the most scientifically advanced. For example, Integra™, perhaps the most widely used substitute is technology that was developed in the early 1980's⁵⁴. On one hand, the reasons for this widespread use are that it is a storable product with a proven track record. On the other hand, the relative cheapness of Integra™ compared to a more advanced cellular product, which is not guaranteed to give superior results, make it the more attractive choice. For a future advanced substitute to become widely used it must produce a therapeutic benefit that justifies the extra cost of its use.

The development of more complex and effective skin substitutes hinges on an increased knowledge of detailed information on the mechanisms of wound healing. Further awareness of the key molecules, and the spatial and temporal action of these during the wound healing process, should sculpt the design of future substitutes. One way to exploit such knowledge would be to engineer cells seeded into the scaffolds to over express certain growth factors and/or cytokines to accelerate the healing process. For the treatment of chronic ulcers, for example, fibroblasts that have been engineered to over express vascular endothelial growth factor (VEGF) or platelet-derived growth factor (PDGF) could be beneficial through promotion of angiogenesis. An alternative method, which is the subject of intensive research, is the construction of bioactive scaffolds. These scaffolds are constructed from, or contain, growth factors and other molecules involved in wound healing. The theory again is to provide the healing wound with molecules that will speed up neotissuegenesis or margin cell migration. One of the main problems with this method is controlling the release of the bioactive molecules. This can be achieved through the designing the scaffold material to control the *in vivo* degradation rate, thus controlling the

release of the bioactive molecules from the scaffold. Growth factors could also be attached to the matrix, as found in the natural tissue. Alternatively the release of bioactive molecules has been controlled by their absorption into gel beads (often alginate) or containment in microspheres¹⁶¹. These are inserted into the scaffold and the bioactive molecule released as the beads or microspheres degrade.

Scarless healing is the ultimate goal in the development and use of skin substitutes. The key to achieving this seems to lie in the study of the embryonic healing process and in the ability of an embryo in the 1st trimester, when experimentally wounded, to heal the injury without the formation of a scar¹⁶². Although this well documented phenomenon has been known for a considerable time, it is still to be determined how embryos achieve this. The challenge facing tissue engineers is to selectively reactivate this ability. Currently it appears that hyaluronan, the immature immune system and the JNK cascade, which is important in the migration of the skin cells in embryonic development and in wounding, are involved in the process¹⁶². Substitutes designed to deliver the crucial identified factors could induce the ability for scar-less regeneration in the cells of post-natal skin.

Another area of interest that is relatively unexplored is the use of designer polymers to shape the biochemical and mechanical properties of scaffolds. Through this technique it may be possible for researchers to closely control physical factors such as degradation rate, tensile strength and flexibility. Additionally, attachment sites like the RGD attachment site could be incorporated into the structure of the polymers within the scaffold. This would allow placement of certain growth factors or selective attachment sites at specific points within the matrix. For example, incorporating VEGF into the dermal portion of the scaffold could encourage vascularization of the substitute, whilst incorporating epidermal growth factor (EGF) into the epidermal region of the scaffold could help to achieve rapid re-epithelialization. With the development of wound healing knowledge, the molecules and attachment sites involved could be fine tuned to optimize the efficiency of the substitute.

Although demonstrated in many cases to be a life saving surgical tool, skin substitutes remain to produce fully functional skin following implantation. The construction of a substitute that can do more than restore the barrier function of the epidermis and limited mechanical integrity to the dermis still represents a considerable challenge. This area has been overlooked as trivial in comparison to the often vital need to close an open wound. However, without the various appendages of the skin, like the pilosebaceous unit and the apocrine sweat glands, substitutes often represent little more than a biological dressing manipulating host cells through the release of cytokines and growth factors. One suggested way to increase the cellular complexity of substitutes is through the use of stem cells, with interest particularly in the identified populations

that reside within the hair follicle¹⁶³. The epidermal stem cells of the bulge region have been shown to be capable of differentiation into not only the cells of the hair follicle but also into inter-follicular keratinocytes¹⁶⁴. Indeed, it is well established that following epidermal injury the bulge cells help to achieve re-epithelialization following migration to the wound bed¹⁶⁵. Similarly a population of nestin expressing stem cells from the outer root sheath of the hair follicle have been shown to differentiate into functional blood vessels and neural cells¹⁶⁶. The successful exploitation of such populations in the future could be beneficial to the creation of a truly biomimetic skin substitute.

The use of viable autologous cells is preferable when creating a cellular skin substitute. However, the problems associated with using autologous cells are difficult to bypass. These include; culture and manufacture time, storage and transport, and cost. These problems must be addressed in addition to the research aims for an effective substitute to become widely utilised. The Intercytex products (inc. ICX-PRO™ and ICX-SKN™) have been designed with these problems in mind. The manufacturing process of these substitutes has several 'Stop' points inserted into it, at which product development can stop, products can be stockpiled and the process re-started when needed¹⁴⁰. The insertion of these points has reduced manufacture time to one week¹⁴⁰. This model could be applied to other substitutes and improved upon further. Lengthier storage times and easier transport of viable tissues is an area that also needs improving.

All skin substitutes suffer from a lack of level 1 evidence into their efficacy, with randomization a key issue. Small or poorly designed studies giving contradictory results make wider interpretation and comparisons difficult to make. This problem is exacerbated by the different conditions in trials, including different wound starting states and even types and by the natural complexity, inter-patient variability of the healing wound and surgeon experience or skill. The available evidence does suggest that skin substitutes are useful tools especially in acute life threatening wounds where rapid closure is required and in chronic treatment resistant ulcers.

CONCLUSION

Tissue engineered skin substitutes in their various forms have aided the treatment of cutaneous injury and benefited patients since the 1980s. Although possibly the most developed of engineered tissues, engineered skin still has considerable room for improvement. The creation of a substitute that can act as truly mimetic skin tissue should not be considered unattainable. It is anticipated that research into the wound healing process, embryonic development, stem cell differentiation and biomaterial design will combine synergistically in the future to enhance skin substitute design.

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Thalidomide

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Thalidomide, or alpha-phthalimido glutarimide, is a racemic glutamic acid derivative synthesized in Germany in 1956 by Kunz, Keller, and Muckter. The compound was introduced to the public, under the names of, “Distaval,” and, “Contergan,” as a nonbarbiturate sedative hypnotic with antiemetic properties and with minimal relative toxicity based on the observation that individuals exposed to accidental or intentional overdose recovered uneventfully. In 1960, Somers¹ described the sedative-hypnotic effects of thalidomide in animal models without the deleterious effects on the cardiac, respiratory, or autonomic nervous system previously observed with barbiturates. Reports of individuals surviving consumption of 1400 mg of thalidomide supported its marketing as a safe drug². In 1960, an open label clinical trial of thalidomide was performed to assess its efficacy as an antiemetic at the Women’s Hospital of Sydney, Australia; however, the trial was terminated in 1961 when Dr. McBride of the Women’s Hospital noted three cases of congenital absence of the radius in three neonates exposed to thalidomide in utero. Overall, 50% of pregnancies spontaneously aborted, and resulted in congenital malformations, particularly phocomelia (congenital partial limb deficits). Consistent with these observations, limb deformities were noted in offspring of New Zealand rabbits fed thalidomide during their 8th to 16th days of pregnancy. Lastly, Dr. Lenz of Hamburg, a pediatrician, documented over 4000 cases of abnormal limb growth to further strengthen the association between thalidomide exposure between the 30th and 40th days of pregnancy and fetal malformations. By the time thalidomide was taken off the market in 1961, over 5000 deformed infants were born in European countries because of its administration.³

This devastating chapter in medical history also marks the birth of the field of Pharmacoepidemiology. Physicians such as Dr. Williams³ quickly made the realization that if, “prompt reporting of the appearance of congenital malformations, with careful records by physicians of the medications given, had been made, the extent of the thalidomide disaster in Europe could have been enormously reduced.” He went on to further set the stage for the field by adding, “this public health procedure of constant surveillance of the incidence of disease must be, in the last analysis, the final protection against a similar great disaster.”

PHARMACOLOGY

Thalidomide is a white, tasteless, crystalline powder. It has a melting point of 271 degrees and is chemically related to bemegride (a-ethyl-a-methylglutarimide) and to glutethimide (8-ethyl-8-phenyl-glutarimide). The substance is further characterized by being sparingly soluble in water, methanol, ethanol, acetone, and glacial acetic acid, but readily soluble in dioxane, dimethyl formamide, and chloroform and insoluble in ether of benzene¹.

Structurally, thalidomide is a glutamic acid derivative with a single chiral center and a racemic mixture of two active enantiomers, S(–) and R(+), that undergo rapid interconversion at physiologic pH. It is a two-ring system with an asymmetric carbon atom link. The left-sided phthalimide ring is responsible for the drug’s anti-inflammatory and immunomodulatory effects, and the right-sided glutarimide ring is hypothesized to be responsible for the drug’s sedative properties. Thalidomide has high oral bioavailability, although absorption is slow and time to maximum plasma concentration of 1-2 mg/L is 3-4 hours after a single oral dose of 200 mg. Thalidomide has a half-life of 5-6 hours. Upon ingestion, it is enzymatically cleaved into more than 12 different metabolites that are quickly eliminated in the urine.⁴

In efforts to find a less toxic derivative, CC-5013, also known as Lenalidomide, and CC-4047, also known as Actimid, 4-amino-glutarimide derivatives of thalidomide were designed by adding an amino group to the fourth carbon of the phthaloyl ring of the parent compound. Both compounds are racemic mixtures of S(–) and R(+) enantiomers. Like thalidomide, they have high oral bioavailability and are renally excreted. The half-life of CC-5013 and CC-4047 are 3 and 7 hours, respectively. They lack significant dose limiting neurologic and sedative toxicities that are associated with thalidomide and have heightened immunomodulatory activity relative to thalidomide. Furthermore, CC-5013 possesses direct antitumor activity and has been noted to be nonteratogenic when tested in rabbits.⁵

MECHANISMS OF ACTION

The mechanisms of action of thalidomide and its derivatives are not entirely clear. Thalidomide and its derivatives

have been shown to have several anti-inflammatory and immunomodulatory properties, as well as, antiangiogenic effects, which are important for their role in inhibition of tumorigenesis.

Inhibition of Neutrophil Chemotaxis

The differential regulation of expression of adhesion molecules by thalidomide alters leukocyte migration and rolling. *In vitro* studies of the effects of thalidomide on polymorphonuclear cells demonstrate a dose-dependent inhibition of neutrophil chemotaxis⁶⁻⁷. Nogueira et al⁸ revealed that, although thalidomide does not alter the expression of adhesion molecules on resting endothelial cells, it inhibits the induction of adhesion molecules on the surface of endothelial cells by endotoxin and inflammatory cytokines including tumor necrosis factor-alpha (TNF- α) and IL-1. Thalidomide is capable of changing the density of TNF- α induced ICAM-1, V-CAM, and E-selectin antigens⁹ as well as IL-1 β and IFN- γ -induced E-selectin¹⁰. Studies have depicted that the drug dose dependently inhibits lipopolysaccharide (LPS)-stimulated and TNF- α -induced leukocyte chemotaxis¹¹. Thalidomide may reduce inflammation in erythema nodosum leprosum by altering neutrophil chemotaxis, while in multiple myeloma and myelodysplastic syndrome thalidomide modifies the tumor microenvironment.

Inhibition of TNF- α Production

TNF- α is an important regulator of other proinflammatory cytokines and leukocyte adhesion molecules. Sarno et al¹² observed elevated TNF- α and IL-1 in serum from leprosy patients suffering from acute inflammatory reactional episodes-erythema nodosum leprosum (ENL). Her study suggested that TNF- α may be a potential target for thalidomide as decreased serum levels of TNF- α were observed in patients given thalidomide and thalidomide was noted to be a highly efficacious drug for the treatment of ENL. These observations prompted further examination of the role of thalidomide on cytokine production. In 1991, thalidomide was shown to partially inhibit LPS-induced TNF- α production by human blood monocytes at comparable therapeutic serum concentrations in successfully treated ENL patients.¹³ Additional studies investigating the role of TNF- α in mediating the clinical manifestations of leprosy, demonstrated a decrease in TNF- α release with concomitant clinical response in those treated with thalidomide.¹⁴ Thalidomide has been shown to accelerate the degradation of TNF- α mRNA transcripts in LPS-stimulated monocytes, which in turn influences the total amount of TNF- α protein released in response to LPS.¹⁵ Cytokine mRNA inhibition has been correlated to resolution of the inflammatory response *in situ*.¹⁶ Thalidomide has also been shown to act on the downstream signaling events of

NF- κ B, a key transcription factor that mediates the effects of various proinflammatory cytokines, such as TNF- α as well as IL-1 β .¹⁷⁻¹⁸ Although there is evidence for TNF- α and its downstream pathways as a target for thalidomide, there are some conflicting reports to suggest otherwise. Thalidomide likely mediates its clinical efficacy by several mechanisms. Inhibition of TNF- α may be a more prominent effect when macrophage production of this cytokine is high; however, in other settings, thalidomide's ability to costimulate T cells to produce cytokines, including TNF- α , may outweigh this inhibitory effect, as has been noted in patients with toxic epidermal necrolysis, sarcoidosis, and scleroderma.¹⁹⁻²³

Modulation of the T cell Response Systems

Thalidomide has been shown to regulate T helper (Th) cell differentiation *in vitro*, promoting Th2 versus Th1-type cytokines, which may suppress TNF- α .²⁴ Thalidomide has a dose-dependent inhibitory effect on mononuclear cell production of the T helper 1 (Th1) cytokines, or IFN- γ , and IL-12.²⁴⁻²⁵ The effect of thalidomide on cytokine production varies according to the nature of the stimulus and the cell type being stimulated. Whereas thalidomide inhibits LPS-induced monocyte IL-12 production, it stimulates the production of IL-12 in T-cell dependent systems. IL-12 has been shown to enhance natural killer cell and T cell activity causing, "immune stimulation."²⁰ Importantly, this increase in natural killer cell cytotoxic activity induced by thalidomide has been shown to augment lysis of human multiple myeloma cell lines, providing a mechanism of action for thalidomide in the treatment of multiple myeloma.²⁶

Thalidomide may also stimulate CD8 T cells.²⁷ CD8 + T cells are vital components of the immune response to foreign antigens. The activation and proliferation of these cells require costimulation of the T-cell receptor by a second signal, usually provided through interaction between surface markers on antigen-presenting cells and their ligands on T-cells. Thalidomide augments the CD8 T-cell response in the absence of a second costimulatory signal.²⁸ Additionally, thalidomide has been found to decrease the T helper to T suppressor cell ratio, boosting regulatory T cell function, another potential immunomodulatory mechanism for the drug.²⁹

Inhibition of Angiogenesis

Thalidomide's potential, as an antineoplastic agent was not fully realized until D'Amato demonstrated the drug's antiangiogenic activity. In 1994, D'Amato³⁰ demonstrated the ability of thalidomide to inhibit neovascularization in rabbits. Thalidomide metabolites have also been shown to inhibit angiogenesis induced by basic fibroblast growth factor (bFGF) and vascular endothelial growth factor

(VEGF) in a rabbit cornea micropocket assay and mouse corneas.³¹ Although this may be partially caused by thalidomide's anti-TNF properties, as TNF- α has been shown to positively influence vessel formation,³² thalidomide has been shown to also independently affect angiogenesis.³¹

Hypnotic Properties

Thalidomide's right-sided glutarimide ring is thought to be responsible for the drug's sedative effects.³³ It is hypothesized that the mechanism involves activation of a sleep center in the forebrain.³⁴ It should be noted that unlike other sedative agents such as barbiturates, ingestion of even extremely high doses of thalidomide has not resulted in fatal outcomes².

FDA-APPROVED USES OF THALIDOMIDE

Erythema Nodosum Leprosum (ENL)

Leprosy, also known as Hansen's disease, is a chronic progressive granulomatous infection of the skin and peripheral nerves caused by *Mycobacterium leprae*, a fastidious, gram positive, intracellular, acid-fast bacillus. Although leprosy is endemic to Asia, Africa, and South America, in 2006, 137 new cases of Hansen's disease were reported in the United States to the National Hansen's Disease Registry, with 63% occurring in California, Florida, Louisiana, Massachusetts, New York, and Texas. Clinical features are determined by the immunologic response to the organism and vary along a spectrum between tuberculoid and lepromatous leprosy. Tuberculoid leprosy is limited to well-defined skin patches and nerve trunks because of a cell-mediated response to the organism. Lepromatous leprosy is characterized by more widespread infiltration of the skin and nerves by the mycobacterium caused by T-cell unresponsiveness, hypothesized to be the result of immune deviation of cytokine production from a Th-1 type to a Th-2 type pattern, deletion of T cells reactive to the organism, and the presence of suppressor T-cell activity. Affected patients have high titers of antibodies to antigens specific to *M. leprae*.

Upon initiation of treatment, the disease can be complicated by the development of immunologically mediated, "reactional states," including type 1 leprosy reactions, also known as reversal reactions, and type 2 reaction, also known as erythema nodosum leprosum (ENL). Type 1 reactions are characterized by painful inflammation of affected areas caused by spontaneous increases in T-cell reactivity to *M. leprae* and the resultant cytokine response. Type 2 reaction, or ENL, occurs only in borderline-lepromatous and lepromatous leprosy states, and is characterized by a systemic inflammatory response syndrome, the development of erythematous skin nodules, and other regions of focal inflammation caused by complement-mediated reactions to extravascular immune complex

deposits. Histologic findings include infiltration of the dermis and subcutaneous tissues with lymphocytes, macrophages, and neutrophils sometimes accompanied by a leukocytoclastic vasculitis.³⁵

In 1965, Israeli dermatologist Jacob Sheskin used thalidomide to treat insomnia in a patient with ENL and unexpectedly discovered that lesions cleared within 48 hours of drug administration.³⁶ Thalidomide, as noted previously, functions as an immune system modulator, although its main mechanism in the treatment of ENL remains unclear. Disease symptomatology has been associated with elevated levels of TNF- α with clinical and pathologic resolution upon treatment with thalidomide and concomitant reduction in levels of TNF- α .³⁷ *In vitro* studies demonstrate profoundly diminished TNF- α production from peripheral blood monocytes in response to *M. leprae* and associated clinical symptom resolution with administration of thalidomide¹⁴. However, the significance of TNF- α in the pathophysiology of ENL is unclear as increases in TNF- α have been observed in patients treated with thalidomide.²⁰ Thalidomide has also been shown to down-regulate expression of adhesion molecules such as ICAM-1 on epidermal keratinocytes and reduce dermal infiltration of neutrophils in ENL, contributing to reduction in the dermal inflammatory response.³⁷

Controlled and open label trials demonstrate the effectiveness of thalidomide for ENL. In a double-blind trial by the World Health Organization comparing thalidomide and acetylsalicylic acid³⁸, 73% of reactions treated with thalidomide resolved by day 8 of treatment versus resolution of 23% of reactions in the acetylsalicylic acid group over a similar time frame. In a worldwide survey, Sheskin reviewed the effects of thalidomide in 4522 patients with ENL and noted that 4479 or 99% of patients improved.³⁹ Thalidomide was recommended by the Fifth International Leprosy Congress in 1973 and the World Health Organization in 1994 as the preferred treatment for moderate to severe ENL in men and women of non-child-bearing potential. In 1998, the United States Food and Drug Administration (FDA) granted approval for the use of thalidomide for the treatment of ENL. Dose recommendations range from 100 mg to 400 mg daily. Observations suggest that discontinuation of treatment, whether it is abruptly or by taper is frequently complicated by disease recurrence, and further studies are needed to establish improved regimens.⁴⁰

Multiple Myeloma

Systematic reviews of clinical trials have highlighted the efficacy of thalidomide in patients with previously untreated⁴¹ or relapsed/refractory multiple myeloma⁴²⁻⁴³ and in May 2006, the FDA granted approval for the use of thalidomide in combination with dexamethasone in patients with newly diagnosed multiple myeloma. Multiple myeloma is a B cell malignancy characterized by accumulation of clonal malignant plasma cells in the bone marrow, suppression of

erythropoiesis and consequent anemia, destructive bony lesions, increased susceptibility to infections, hypercalcemia, and renal insufficiency caused by accumulation of light chains of the monoclonal myeloma immunoglobulin in renal tubules. It is the second most common hematologic malignancy. Per the National Cancer Institute's SEER Cancer Statistics Review, based on data from 2002-2006, the age-adjusted incidence rate of multiple myeloma is estimated at 5.6 per 100,000 men and women, with an overall 5-year survival rate of 37.1%.

Recognition of thalidomide's teratogenic properties instigated studies of its effects in patients with cancer. The drug's potential as an antineoplastic agent became more apparent upon D'Amato's demonstration of its antiangiogenic activity. Prominent bone marrow vascularization is known to be positively correlated with increased myeloma activity. Additionally, levels of cytokines that promote angiogenesis, including beta fibroblastic growth factor (bFGF) and vascular endothelial growth factor (VEGF) are elevated in affected patients. This prompted Singhal et al⁴⁴ to test the role of thalidomide as a single agent in 84 patients with relapsed and refractory multiple myeloma. The response was defined as a decline in the level of serum or urine paraprotein of at least 25% on two occasions at least 6 weeks apart. A response rate of 32% was observed, including two complete remissions, triggering further interest in the study of thalidomide in multiple myeloma.

Further studies also confirm that increased bone marrow angiogenesis in multiple myeloma is caused by increased expression of bFGF and VEGF.⁴⁵ Patients responding to thalidomide do have a significant decrease in marrow microvascular density, although microvessel density does not necessarily predict clinical response to thalidomide.⁴⁶

Tumor and microenvironment interactions are critical in the pathophysiology of multiple myeloma.⁴⁷ Adhesion of multiple myeloma cells to bone marrow stromal cells via adhesion molecules⁴⁸ mediate proliferation of the malignant clone via stimulation of intracellular signaling pathways and subsequent release of paracrine and autocrine cytokines⁴⁹ and growth factors,⁵⁰ including VEGF. Production of osteoclastogenic cytokines uncouples the regulatory mechanisms for bone formation and bone resorption and results in the clinical sequelae of the malignancy. In addition, certain cytokines, such as IL-6, function as growth stimuli for the malignant clone, via activation of the NF-κB anti-apoptotic signaling cascade, fostering a vicious cycle of bone resorption and tumor growth.⁵¹ Bone marrow stromal cells and plasma cells isolated from multiple myeloma patients have also been shown to express TNF-α.⁵² In 2001, Hideshima et al. demonstrated that TNF-α directly stimulates IL-6 production in bone marrow stromal cells and up-regulates expression of adhesion molecules on myeloma and bone marrow stromal cells, thereby augmenting tumor microenvironment interactions and promoting tumor growth.⁵³ Additionally,

certain cytokines such as IFN-γ inhibit IL-6-dependent proliferation of myeloma cells.⁵⁴ Therefore, thalidomide's anti-inflammatory and immunomodulatory activities, including its anti-TNF activity and costimulation of CD8 T cells with resultant IFN-γ production and specific anti-tumor T cell cytotoxicity, likely all contribute to promote disease stasis or reduction in affected patients.

Myelodysplastic Syndromes

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal hematopoietic stem cell disorders characterized by ineffective hematopoiesis and pancytopenias, with affected patients having an increased risk of disease transformation into acute myeloid leukemia (AML). One of the more common chromosomal abnormalities associated with MDS is deletion of chromosome 5. Patients with a 5q deletion have a distinct hematologic profile, including macrocytic anemia, normal to increased platelet count, mild leukopenia, hypolobulated megakaryocytes in the bone marrow and medullary blast count of <5%. Those with an isolated 5q deletion have a better prognosis than patients with multiple chromosomal abnormalities.

The immunomodulatory activities of thalidomide and its derivatives including T-cell costimulation, augmentation of natural killer cell cytotoxicity, suppression of hematopoietic inhibitory cytokines, inhibition of angiogenesis and endothelial cell adhesion and migration in the tumor microenvironment, as well as direct proapoptotic effects of the thalidomide derivative, lenalidomide, to deletion 5q clones all contribute to the antitumor response seen with administration of these medications. In phase II clinical trials with thalidomide, although a hematopoietic response has been noted, patients have required prolonged drug treatment and toxicity-related discontinuation is prominent.

An international phase II trial of lenalidomide (MDS-003) at a dose of 10 mg daily in 148 patients with 5q- MDS, resulted in transfusion independence in 67% of the subjects studied, and an additional 9% had a 50% or greater decrease in the number of transfusion required while being treated. Approximately 45% of the subjects studied demonstrated a complete cytogenetic response.⁵⁵

In December of 2005, lenalidomide was approved by the U.S. Food and Drug Administration for the treatment of patients with low-risk to intermediate risk MDS with deletion 5q, with or without additional chromosomal abnormalities at a dose of 10 mg daily. Patients with more complex cytogenetics are eligible for treatment, only if they have no more than one cytopenia and a medullary blast count of less than 5%.

Nonplasma Cell Malignancies

The role of thalidomide in the treatment of solid tumors is currently under investigation and is thoroughly detailed

in a review by Kumar et al.⁵⁶ The drug has shown variable promise. In patients with malignant melanoma, breast cancer, or high-grade brain gliomas, thalidomide alone has not been shown to be efficacious; however, its role when combined with other chemotherapeutic agents is yet to be more clearly delineated. Thalidomide has shown more promise when used in patients with renal cell carcinoma, Kaposi's sarcoma, prostate cancer, in combination with irinotecan in patients with metastatic colorectal cancer, unresectable hepatocellular carcinoma, malignant mesothelioma, small cell lung carcinoma, and metastatic neuroendocrine tumors. However, more data is needed for any statements supporting the use of thalidomide in the treatment of any of these malignancies.

ADDITIONAL USES OF THALIDOMIDE AND THALIDOMIDE DERIVATIVES

Thalidomide has been introduced for treatment of a variety of disease states associated with immune system dysfunction. Serious adverse effects including teratogenicity and irreversible peripheral neuropathy have precluded FDA approval as well as restricted its use to recalcitrant conditions only.

Aphthous Stomatitis

Aphthous ulcers are self-limited shallow, painful lesions caused by destruction of poorly keratinized surfaces of the oral mucosa. Although the initiating factor is unclear, immunologic dysfunction has been hypothesized to play a role. Studies have demonstrated enhanced neutrophil chemotaxis, increased TNF-alpha production, and a decreased CD4 to CD8 ratio in affected patients.⁵⁷ Thalidomide was first applied towards treatment of aphthous ulcers in 1979 when six males with recurrent and necrotic mucocutaneous refractory aphthae were given 100 mg of thalidomide daily. The ulcers healed in 7-10 days with occasional recurrences after the medication was discontinued.⁵⁸

Several studies thereafter, have demonstrated the efficacy of thalidomide in the treatment of this condition. In an open label clinical trial with 40 patients treated with 100 to 300 mg of thalidomide daily for 3 months, 34% were cured and the rest showed a marked clinical improvement.⁵⁹ In a multicentered, randomized, crossover study of 100 mg of thalidomide daily versus placebo in 73 patients, 32 patients treated with thalidomide experienced complete remission in the treatment group compared to six patients in the placebo group.⁶⁰ In an open label trial comparing thalidomide to other immunomodulatory agents including dapsone, colchicine, and pentoxifylline, thalidomide was noted to be the most efficacious and most tolerable.⁶¹ Further studies evaluating the efficacy of lower doses of thalidomide will be important.

Thalidomide also appears to be highly effective in the treatment of HIV-associated aphthous ulcerations.

In a double blind, randomized, placebo-controlled study, patients received a four-week course of either 200 mg of thalidomide or placebo orally once per day. Fifty-five percent of the thalidomide group had complete healing of their aphthous ulcers after 4 weeks versus 7% in the placebo group. Patients in the thalidomide group also experienced improvement in quality of life measures such as discomfort with oral intake.⁶² However, in this study, patients in the thalidomide group had an increase in their viral load and although additional studies have not detected significant increases in viral loads or changes in CD4 T cell counts,⁶³⁻⁶⁴ thalidomide should be used cautiously in patients with HIV. Additionally, thalidomide in low intermittent maintenance doses does not successfully treat recurrence of HIV-associated ulcers in patients who had previously responded to the drug.⁶⁵

HIV-Associated Wasting

HIV-associated weight loss often manifests itself in patients with advanced disease. It occurs secondary to decreased appetite and decreased caloric intake, malabsorption, and chronic diarrhea, frequently caused by microsporidial infections, cytokine effects, and endocrine dysfunction and has a high morbidity and associated mortality if not adequately treated.⁶⁶ In a double-blind, placebo-controlled trial, thalidomide was randomized at 100 mg/day or 200 mg/day versus placebo for 8 weeks. Patients in the two thalidomide groups were noted to have significant increase in their weight, half of which was noted to be fat-free mass.⁶⁴ Thalidomide has also been shown to be effective in treatment of microsporidiosis-associated diarrhea.⁶⁷ Although thalidomide carries significant dose-limiting toxicities, it has been shown to be beneficial in the treatment of HIV-associated wasting.

Behçet's Syndrome

Behçet's syndrome is a chronic, relapsing, multisystem disease of unclear etiology characterized by a triad of aphthous stomatitis, genital ulcerations, and uveitis. Immune complex-mediated vascular damage and immune dysregulation has been implicated in the pathogenesis of the disease although the exact mechanism of action is unclear.⁶⁸ Thalidomide use in Behçet's syndrome was first reported in 1982. Patients with symptoms refractory to other immunomodulatory medications were given 400 mg/day of thalidomide for 5 days, followed by 100 mg twice a day for 15 to 60 days. The majority of patients had resolution of orogenital lesions.⁶⁹

Several studies thereafter, sought to demonstrate the efficacy of thalidomide in patients with Behçet's disease. A randomized, double-blind, placebo-controlled trial depicted a complete mucocutaneous response in two out of 32 patients treated with 100 mg/day of thalidomide, in five out of 31 patients treated with 300 mg/day

of thalidomide, and in 0 out of 32 patients who received placebo.⁷⁰ Oral manifestations improved after 4 weeks of treatment and genital ulcers improved after 8 weeks of treatment. Thalidomide treatment significantly increased development of erythema nodosum skin lesions during the first 8 weeks of the trial, but with continued treatment, the frequency in the treatment and placebo groups was similar. Discontinuation of treatment resulted in relapse of mucocutaneous lesions. Somnolence, neuropathy, and constipation were noted to be the most frequent limiting toxicities, however, lower doses of thalidomide have been observed to be effective and have fewer side effects.⁷¹ Additionally, case reports describe the successful use of thalidomide for the relief of other systemic manifestations of Behçet's disease, including arthritis, pyoderma gangrenosum, neuro-Behçet's, and colitis.⁷² Further studies are necessary to establish the disease-modifying power of thalidomide in Behçet's syndrome.

Graft-Versus-Host Disease

Graft versus host disease has a significant impact on morbidity and mortality after an allogeneic stem cell transplant. Although thalidomide does not appear to be of benefit in acute GVHD, it has been shown to be of some benefit in refractory chronic GVHD in conjunction with other immunosuppressive agents at doses of 600-1200 mg per day.⁷³ A randomized trial, however, demonstrated significant toxicity, particularly neurologic side effects, at the doses that have been used to ameliorate disease symptoms.⁷⁴ Moreover, thalidomide does not add benefit when incorporated into the initial therapy for chronic GVHD. Thalidomide is therefore, reserved for salvage therapy for refractory chronic GVHD.⁷⁵

Jessner-Kanof Lymphocytic Infiltration of the Skin

This benign chronic disorder is characterized by smooth, erythematous, and asymptomatic papules, or plaques secondary to T cell infiltration. Thalidomide was first used to treat this entity in an open label trial in 1983.⁷⁶ In a prospective, multicenter, double-blind, crossover study in 1995, a statistically significant response was noted in patients treated with thalidomide at 100 mg/day over 2 months.⁷⁷

Uremic Pruritus

Inflammation appears to be an important contributor to pruritus in patients with end stage renal disease.⁷⁸ Based on the observation that thalidomide alleviated pruritus in a dialysis patient with leprosy, investigators conducted a randomized, double-blind, crossover trial evaluating the efficacy of thalidomide for pruritus associated with uremia.

Twenty-nine patients with refractory uremic pruritus were treated with thalidomide at 100 mg/day for one week versus placebo. Over 60% of patients experienced an 80% reduction in symptoms.⁷⁹

Cutaneous Lupus Erythematosus

Thalidomide is indicated in patients with refractory severe cutaneous manifestations of lupus. In 1983, thalidomide was studied in 60 patients with chronic discoid lupus erythematosus, refractory to topical steroids and antimalarials. Initially, patients were prescribed 400 mg/day of the medication, but this was reduced to 50-100 mg/day and 90% of patients experienced complete or significant disease regression in a two-week period. Although treatment discontinuation led to disease recurrence in a majority of patients, a clinical response was obtained with repeat courses of thalidomide.⁸⁰ Lower starting doses of thalidomide (50-200 mg/day) and maintenance doses of 25 mg/day have been shown to be efficacious⁸¹, although a high incidence of neurotoxicity has been reported even with low-dose therapy.⁸² Further studies also support the initial findings of relapse after discontinuation of therapy.

Prurigo Nodularis

Prurigo nodularis is a chronic inflammatory dermatosis of unclear etiology characterized by pruritic, symmetric, papulonodular lesions on the extensor surfaces of extremities. Although initial reports demonstrate efficacy at doses of 200 mg/day,⁸³⁻⁸⁴ case reports of success with lower doses of thalidomide (100 mg/day starting dose for 1 month, and thereafter, 50 mg and 100 mg/day on alternate days) are published.⁸⁵ Additionally, an excellent response and minimal side effects were seen in an open trial combining thalidomide as initial therapy, followed by narrow-band UVB radiation.⁸⁶ In addition, of note, an uncontrolled case series found thalidomide to be effective for the treatment of prurigo nodularis in patients with HIV, in whom prurigo nodularis tends to be refractory to other forms of treatment.⁸⁷

Actinic Prurigo

Actinic prurigo is a photodermatosis that occurs mostly in Mestizo, or mixed Native American and European women and is characterized clinically by macules, papules, crusts, hyperpigmentation, and lichenification. Skin lesions are thought to develop because of increased TNF-alpha production in response to UV light in genetically predisposed individuals. The clinical response seen with thalidomide has been correlated with a reduction in serum TNF-alpha levels and modulation of IFN-gamma and CD3 positive T cells.⁸⁸ Thalidomide was first used to treat actinic

prurigo in 1973.⁸⁹ Observational studies since then have confirmed the drug's efficacy in treatment of this disease. Case reports describe success with low doses of thalidomide⁹⁰ and have demonstrated its safe use for long-term disease suppression at these doses⁹¹.

Adult Langerhans' Cell Histiocytosis

This rare disorder is characterized by abnormal proliferation and dissemination of histiocytes, cells that are almost identical in physical and functional properties to normal dendritic cells of the immune system. The disease is thought to result from an inappropriate immune response to antigens or an appropriate response to abnormal signals from other immune cells, as lesions have aggregates of other immunologically active cells, decreased numbers of suppressor T lymphocytes, and increased levels of inflammatory cytokines including TNF- α .⁹² Thalidomide was first used to treat histiocytic lesions in 1987 at doses of 50 mg/day, followed by 50 mg every other day for disease suppression.⁹³ In 1992, a 29-year-old female was treated with thalidomide at doses of 100 mg/day for 3 months for histiocytic infiltration of the parotid gland; however, in this case, no improvement was noted in the cutaneous manifestations of the disease and treatment had to be discontinued because of development of neuropathy.⁹⁴ Further reports document remission of cutaneous manifestations, with recurrence after discontinuation of thalidomide therapy, but with subsequent remission after reintroduction of treatment.⁹⁵ Case reports also describe the efficacy of thalidomide for treatment of mucocutaneous as well as hypothalamic disease manifestations, including diabetes insipidus.⁹⁶⁻⁹⁸ In a phase II clinical trial⁹⁹, thalidomide was noted to be effective in patients considered low risk, or those with bone, skin, pituitary, or neurologic spread; however, it did not elicit a significant response in patients with involvement of the spleen, liver, lung, or bone marrow.

Sarcoidosis

Sarcoidosis is a granulomatous multisystem disorder of unknown etiology. Granulomas form because of an immunologic response to an unknown antigenic trigger in genetically predisposed individuals. T cell activation and associated macrophage activation with subsequent release of cytokines such as TNF- α lead to granuloma formation.¹⁰⁰ Thalidomide was first used to treat two patients with steroid refractory cutaneous sarcoidosis and two patients with cutaneous and pulmonary involvement in 1983.¹⁰¹ Since then, several case reports have been published that demonstrate the efficacy of low-dose thalidomide (50-400 mg/day) in treatment of cutaneous lesions.¹⁰² Thalidomide has also reportedly been successfully implemented in the treatment of pulmonary¹⁰²⁻¹⁰³ and neurologic¹⁰⁴⁻¹⁰⁵ manifestations of sarcoidosis.

Erythema Multiforme

Erythema multiforme is a hypersensitivity reaction in response to infectious or chemical agents that clinically appears as a symmetrically distributed polymorphous eruption consisting of macules, papules, and target lesions, with minimal mucosal involvement. IFN- γ -induced inflammatory cascades as well as TNF- α expression in response to specific antigenic triggers are responsible for disease pathogenesis. There are several anecdotal reports of persistent¹⁰⁶⁻¹⁰⁷ and recurrent¹⁰⁸⁻¹⁰⁹ erythema multiforme successfully treated with thalidomide. A retrospective study of 26 patients with chronic erythema multiforme refractory to typical agents including acyclovir and prednisone, demonstrates a reduction in disease duration and disease remission in patients treated with 100 mg of thalidomide daily.¹¹⁰

Lichen Planus and Lichen Planopilaris

Lichen planus of the skin is a pruritic, papular, polygonal, and violaceous eruption often covered with lacy appearing white striae (i.e., Wickham's striae). It typically afflicts the wrists and the ankles, although it can affect any part of the body including the genitals, scalp, and nails. Follicular lichen planus is also known as lichen planopilaris. Mucosal lichen planus may present as painless white streaks in a lacy pattern, painful ulcerations, or as erosive lesions on the tongue, lips, buccal, or genital mucosa.

Histopathologic findings of T lymphocyte-mediated epidermal damage suggest that the disease is secondary to a cell-mediated response to an unknown antigenic trigger. Lichen planus has been associated with other autoimmune diseases and infectious agents such as hepatitis.

The efficacy of thalidomide in treating lichen planus and lichen planopilaris is controversial and no controlled trials are reported. Case reports demonstrate the efficacy of thalidomide in treatment of erosive lichen planus at doses ranging from 25 mg to 300 mg daily, however, treatment-limited toxicities led to eventual discontinuation of the drug.¹¹¹⁻¹¹⁴ In a 6 month open label trial, six patients with lichen planopilaris were treated initially with 100 mg/day of thalidomide for 1 month and then 200 mg/day thereafter depending on the initial response. The results depicted no clinical benefit of thalidomide in treatment of lichen planopilaris.¹¹⁵

ADVERSE EFFECTS

Teratogenicity

The most serious adverse property of thalidomide is its teratogenicity. Teratogenic effects have been observed after a single dose of 200 mg on the fortieth day of pregnancy. There are several proposed mechanisms for this. Thalidomide may block transmission of a signal from the mesonephros

that is necessary for normal limb development.¹¹⁶ The drug's antiangiogenic properties likely also play a role. Additionally, thalidomide causes free radical-mediated damage to DNA and other cellular macro-molecules.¹¹⁷

In efforts to prevent teratogenic events, the drug is marketed via the S.T.E.P.S. (System for Thalidomide Education and Prescribing Safety) program. Women of childbearing potential must undergo a pregnancy test prior to starting therapy and every 2 to 4 weeks during treatment. Women of childbearing potential must use two contraceptive modes starting 4 weeks prior to treatment onset, and must continue this for 1 month following the last dose of the drug, or remain abstinent over this same time course. Breastfeeding over this period is contraindicated. Males must abstain from sexual activity or use a condom. Patients and prescribers must sign an informed consent form prior to initiating treatment and complete questionnaires over the course of treatment in efforts to reiterate the drug's teratogenic potential.

Neurotoxicity

Thalidomide's neurotoxic effects have been well characterized and are significant dose limiting toxicities of the medication. Painful paresthesias of the hands and feet and proximal muscle weakness became apparent as clinically significant, possibly irreversible, effects of thalidomide therapy in the 1960s. Although duration of treatment has been purported to affect the severity of symptoms, other studies contradict this finding, although the size of the dose itself does appear to be a factor, with higher doses causing disability earlier in the course of therapy. Nerve conduction studies are suggestive of an axonal neuropathy and sural nerve biopsies demonstrate patterns of Wallerian degeneration and selective loss of large diameter fibers.¹¹⁸ In a study of 22 patients suffering from thalidomide neuropathy who were followed out 4 to 6 years after stopping drug therapy, 50% of patients continued to suffer without improvement in symptomatology, and those who improved experienced a very slow recovery.¹¹⁹ Peripheral neuropathy has been shown to be the most common cause for discontinuation of therapy.¹²⁰

Pretreatment electrophysiologic testing of sensory nerve action potential amplitudes and repeat testing after each 10-gram increment in the total dose of thalidomide or on a biannual basis has been suggested. A fall from the baseline score of greater than 40% should prompt reduction or discontinuation of thalidomide therapy as sensory loss may be severe and permanent.¹²¹

Venous Thromboembolic Events (VTE)

Although this is a less frequent side effect of treatment, several reports have presented a statistically significant association between the use of thalidomide and

thalidomide derivatives and the development of VTEs, particularly in patients with an underlying procoagulant state such as a malignancy. Generation of apoptotic cells, endothelial damage, and production of IL-2 and IFN- γ from thalidomide therapy foster a thrombogenic environment. A recent meta-analysis evaluated the risk of VTEs in 3,322 multiple myeloma patients receiving treatment and found that thalidomide increased the risk of thromboembolic events by 2.6 times, dexamethasone increased the risk by 2.8 times, and thalidomide/dexamethasone combination treatment increased the risk by eight times. Prophylactic doses of low-molecular-weight heparin or warfarin titrated to achieve a therapeutic international normalized ratio (INR) significantly reduced the risk of VTEs in this patient population.¹²²

Other Adverse Effects

The most common side effect associated with thalidomide treatment is somnolence, however, this may resolve after 2 to 4 weeks of treatment. Other side effects include constipation, depression, headache, nausea, weight gain, edema, transient papular or vesicular rashes, and subclinical hypothyroidism.¹²³

What We Know

- Thalidomide is a racemic glutamic acid derivative with anti-inflammatory, anti-angiogenic, immunomodulatory, and hypno-sedative properties.
- Lenalidomide and Actimid are less toxic 4-amino-glutarimide derivatives of thalidomide.
- Thalidomide is FDA approved for the treatment of erythema nodosum leprosum (ENL), multiple myeloma, in combination with dexamethasone, and low to intermediate risk myelodysplastic syndrome with deletion 5q.
- The use of thalidomide for non-plasma cell malignancies is currently under investigation.
- Thalidomide has been used for the treatment of a variety of disease states associated with immune system dysfunction that are refractory to other immunomodulating therapies.
- Thalidomide is a teratogen. In utero exposure results in congenital malformations, particularly phocomelia, or partial limb deficits. Patients and prescribers must be enrolled in the S.T.E.P.S. program.
- Serious adverse effects include irreversible neuropathy and venous thromboembolic events.

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Percutaneous Hormone Transfer

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INTRODUCTION

Transdermal hormone application is becoming an increasingly popular form of therapy, given the percutaneous route allows for the use of fewer hormones and avoids the potential side-effects associated with first pass metabolism. However, topically applying hormones may result in skin-to-skin transfer of the bioactive chemical from the patient to an unintended subject, like the patient's partner or family member. There have been documented cases of skin-to-skin transfer of testosterone creams from a father, the patient, to his son causing precocious puberty.¹⁻⁶ Given the potential harm from topical hormone use, investigation of percutaneous hormone transfer is needed.

METHODS

We conducted a systematic search in Scopus using keywords "estrogen" and "skin transfer." A second search was con-

ducted in Scopus using keywords "testosterone" and "skin transfer." The search was limited to articles published in the English language up until February 2, 2010.

RESULTS

Four articles studied skin-to-skin transfer of estrogen. Three of the four involved the transfer of estrogen *in vivo* from healthy women to naive recipients. One article was excluded because it studied absorption of estrogen *in vitro*⁷. The details of the three articles are in Table 68-1.

Schumacher studied the skin-to-skin transfer of estradiol from 20 postmenopausal women to 20 healthy men. They used an estradiol metered-dose transdermal spray (Evamist) to apply the hormone on the women's skin. The women had their inner forearms sprayed and 1 hour after application, they held their forearms tightly against the inner forearm of the untreated men with no rubbing

TABLE 68-1—Estrogen

	Schumacher	Wester	Taylor
Subjects	20 postmenopausal women	6 postmenopausal women	14 postmenopausal women
Naïve transfer recipients	20 healthy men	6 healthy men and women	14 male partners
<i>Skin application</i>			
Formulation	Transdermal spray	Gel (oestrogel)	Topical emulsion (Estrasorb)
Daily dose of estradiol (mg)	4.59	5	8.7
Location	forearm	forearm	leg
<i>Exposures</i>			
No. of exposures/day	1	1	2
Duration of exposure (days)	1	1	2
<i>Skin-to-skin contact</i>			
Time after application (hrs)	1	1	2 and 8
Vigorous (min/exposure)	0	10 strokes	2
Gentle/no movement (min/exposure)	5	15	0
Results	AUC 0-24 (pg·hr/mL) Pre-contact (arithmetic mean)= 550.9 Post-contact= 572.2 C avg (pg/mL) Pre-contact= 27.7 Post-contact= 29.6	% dose still on skin= 2.3 +/- 2.0	AUC 0-24 (pg·hr/mL) Pre-contact= 407.3 Post-contact (Day 2)= 504.6 C avg (pg/mL) Pre-contact= 17 Post-contact (Day 2)= 21
Comments	Sig transfer did not occur	Transfer occurred	Sig transfer occurred

or movement for 5 minutes. Blood samples were collected from the men at specified timed intervals after contact and compared to precontact blood samples. Estradiol levels were determined by calculating the area under the concentration-time curve (AUC) from time 0-24 hours. From precontact to postcontact, the AUC increased from 550.9 pg·hr/mL to 572.2 pg·hr/mL. However, the 90% CI of the ratios of AUC was 1.00 to 1.07, which was within the prespecified equivalence range of 0.8-1.25. Therefore, the conclusion was made that significant transfer of estradiol via skin-to-skin contact did not occur.

Wester examined skin transfer of estradiol via a gel formulation (oestrogel) was determined between six postmenopausal women and six healthy recipients, both men and women. A single dose of ¹⁴C labeled estradiol was applied to the inner forearm of postmenopausal women and after 1 hour of air drying the women rubbed their forearms against the naive recipients. After contact, urine samples were collected from the recipients at timed intervals. The amount of estradiol on the skin of the recipients was calculated as a percentage of the original dose applied to the women subjects, with the thought that the amount remaining on the skin equaled the amount that was transferred. The results showed that 2.3% of the original dose was still on the skin of the recipients, and therefore the

conclusion was made that skin-to-skin transfer of topical estrogen can occur.

Taylor and Gutierrez studied 14 postmenopausal women who had a single dose of estradiol applied to their legs via an estradiol topical emulsion (estraserb). Two hours after application, on 2 consecutive days, their male partners vigorously rubbed their forearms against the application site on the women's legs. Blood samples were then collected from the men at timed intervals to determine estradiol serum levels. The results showed an increase of the average serum estradiol concentration (Cavg) from precontact to postcontact on day 2 by 25%. Although this increase was statistically significant, all levels were still under the upper limit of the normal range for men (<45 pg/mL).

For testosterone skin transfer, we found two articles involving skin-to-skin or skin-to-clothing transfer. The details of the testosterone articles are listed in Table 68-2. Mazer et al. studied the transfer of testosterone from a patch and a gel formulation to a t-shirt. The subjects were 28 hypogonadal men who had testosterone applied to their abdomen via one of two techniques: a patch (Androderm) or a gel (AndroGel). Their t-shirts were then analyzed on two occasions, 7 days apart, to determine the amount of testosterone that was transferred from their skin to their clothing. Results showed an average transfer of 54.9 µg

TABLE 68-2—Testosterone

	Mazer	Rolf	Rolf
Subjects	28 hypogonadal men	12 healthy men	14 healthy men
Recipient	t-shirt	Themselves	14 artificially hypogonadal men
Skin application			
Formulation	Androderm vs. AndroGel	2.5% gel	2.5% gel
Daily dose of testosterone	Androderm (5mg/d) AndroGel (5g)	0.4g	5g
Location	Abdomen	Inner forearm	Inner forearm
Exposures			
No. of exposures/day	1	1	1
Duration of exposure	14 days	30 min	10 min
Skin-to-skin contact			
Time after application	Day 7, Day 14	30 min	10 min
Vigorous (min/exposure)	0	5	10
Gentle/no movement (min/exposure)	0	0	0
Results	Amount of testosterone extracted from t-shirt (µg) Pre-contact= 1.20 Patch Post-contact (avg Day 7 and 14)= 54.9 Gel Post-contact (avg Day 7 and 14)= 7049.6	% of applied testosterone recovered = 3.1 +/- 1.8	Testosterone serum concentrations (nmol/l) Mean= 2.4
Comments	Sig transfer occurred from subjects to t-shirts, with gel > patch	Transfer occurred	No sig increase in serum testosterone levels occurred

from precontact to postcontact for the patch and 7049.6 µg for the gel. This correlated with a 58-fold increase over the amount extracted at baseline for the patch and 15,000-fold increase for the gel, clearly showing that transfer of testosterone from skin to clothing occurred.

Rolf et al. investigated two separate procedures: the transfer of testosterone interpersonally, from the left forearm to the right forearm of the same subject, and the transfer of testosterone from subject to recipient. The study used a newly developed 2.5% testosterone gel preparation to investigate the transfer of testosterone via skin contact. Results were given by the percentage of applied testosterone recovered at the recipient site. For interpersonal contact, results showed that 3.1% of the dose applied was recovered from the recipient site. For the second part of the study, involving healthy male subjects, there was no increase in serum testosterone levels in the recipients indicating significant transfer of testosterone did not occur.

DISCUSSION

The articles regarding estrogen transfer are difficult to compare because each used various estrogen formulations, at varying doses and had different exposure methods. Of the three articles, the Wester and Taylor papers showed that significant transfer of estrogen from subject to naïve recipient occurred. However, the Schumacher paper did not show significant transfer. Possible explanations for why transfer did not occur may involve the method of skin-to-skin contact used. Both the Wester and Taylor studies involved vigorous skin-to-skin contact, whereas the Schumacher study used no movement during skin-to-skin contact.

Examining testosterone transfer is also difficult because testosterone formulations come in the form of different salts. In addition to differing formulation, dosing and method of transfer, the baseline characteristics including baseline testosterone levels were different between the two studies. The Mazer paper showed that transfer of testosterone could occur from both a testosterone spray and gel formulation onto clothing, with gel transferring a greater amount. The Rolf article showed significant interpersonal transfer but no transfer between subject and recipient.

The skin contains a substantial amount of water and lipid, along with a smaller amount of protein. The stratum corneum specifically contains the following lipids: free sterols, free fatty acids, triglycerides, and sphingolipids. The lipid component of the skin is an important regulator of skin permeability, and is therefore an important factor when considering the skin transfer of chemicals. The solubility of estrogen and testosterone differ depending on the substance they are in. In water, estradiol is practically insoluble with a solubility of 1.51 mg/L. The solubility of testosterone in water at 20°C is 66 µg/mL. In future research, the study of skin-to-skin transfer of hormones should relate to the amount of water and lipid found in the skin.

Transdermal hormone delivery has the potential to offer safer and more effective drug therapy to patients. However, due to the possibility of skin-to-skin transfer of the bioactive chemical, careful and standardized evaluation of percutaneous hormone therapy is necessary. In the broad sense, the topic of skin transfer and permeability is important not only for drugs, but also for toxins that can be used in chemical warfare agents.

CONCLUSION

Skin transfer of hormones is an important and relevant topic that has not been studied extensively. Further investigation of percutaneous hormone transfer is needed to ensure safe usage of topical hormone applications.

What We Know

- Topical hormone transfer is difficult to study and compare because the formulation, dosing and exposure methods vary.
- Of the three estrogen studies, two showed significant transfer of estrogen between subject and naïve recipient.
- Of the two testosterone articles, one showed significant transfer of testosterone from subjects to their clothing.
- Transdermal hormone delivery has the potential to offer safer and more effective drug therapy to patients. However, due to the possibility of skin-to-skin transfer of the bioactive chemical, careful and standardized evaluation of percutaneous hormone therapy is necessary.

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V

Cost Effectiveness Studies



Cost-Effectiveness of Psoriasis Treatments

69

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INTRODUCTION

Psoriasis is a common skin condition affecting 1-2% of the general population. It is associated with significant morbidity that is exacerbated by its chronic and cyclical nature. Psoriasis affects approximately 7 million people in the United States, with an estimated 17% of these patients affected by moderate to severe forms of psoriasis.¹ Furthermore, the annual incidence of concomitant psoriatic arthritis ranges from 1 to 420 (median 180) cases per 100,000² or 6 to 30% of patients.^{3,4} Annual direct health-care and indirect costs (lost work days) are estimated at greater than US \$1500 per person per year (or US \$11.25 billion per year).⁵

The number of therapeutic agents for psoriasis and psoriatic arthritis has increased substantially in the past 10 years and this has led to considerable changes in the standard of care for patients with psoriasis, especially for patients with moderate to severe chronic plaque form of the disease.

Over the past decade, biologically engineered agents from recombinant DNA (i.e., biologics) with specific targets in the immune pathway of psoriasis have emerged into the mainstream pharmaceutical market. These agents have the potential to offer a much improved quality of life in addition to the potential to improve psoriatic arthritis.⁶ While biologics, in general, tend to be as or more effective than traditional therapies for psoriasis, such as topical agents (e.g., corticosteroids, vitamin D analogues and retinoids), phototherapy, and conventional systemic agents (e.g., methotrexate, cyclosporine and oral retinoids), the cost burden of biologics is extremely high. In addition to the high costs of biologics, further costs of regular monitoring and follow-up also need to be included in any accounting.

For mild disease, topical calcipotriol, and its combination with topical steroids are the main recent additions to the armamentarium. Economic analyses of topical treatments have also been published and, in some cases, such as the combination of betamethasone and calcipotriol, treatment can be very expensive if the body surface area (BSA) affected is large.

Fortunately, a number of studies evaluating cost-effectiveness and cost-utility have increased in the past years, allowing comparison between treatment options. Given that head-to-head trials are very expensive and

require large sample sizes, they are rarely performed and, therefore cost-effectiveness analyses generally use multiple studies with similar outcomes and models based on several assumptions.

Several pre- and post-treatment outcome measures are commonly employed to determine the impact of psoriasis on physical and psychosocial function. According to the National Psoriasis Foundation (NPF), psoriasis severity in the context of BSA is defined as mild (BSA <3%), moderate (BSA 3-10%) and severe (BSA >10%).³ The Psoriasis Area and Severity Index (PASI) is a more specific and refined measure of BSA and severity; it is widely used in clinical trials for psoriasis. A PASI score ≥10% is a frequent entry criteria for moderate to severe psoriasis. Most clinical studies define a “responder” with a PASI 75 (75% improvement compared to baseline) and while a “nonresponder” would have less than PASI 50 (50% improvement compared to baseline). Although PASI 75 is an excellent clinical outcome,⁷ PASI scores are still unable to account for the full impact of physical symptoms or limitations (i.e., facial, genital, palmar, and plantar psoriasis, etc), psychosocial factors, and overall quality of life. Health-Related Quality of Life (HRQL) outcome measures account for physical, psychosocial, and occupational impact of various disease states. Examples of relevant indices are Dermatology Quality of Life Index (DLQI) and Dermatology Quality of Life Scales (DQOLS), which are capable of population-specific measurements. More specific indices for disease-specific states include Psoriasis Disability Index (PDI) and Psoriasis Disability Scale (PDS).

Another important outcome for psoriasis research is quality-adjusted life-years (QALYs). QALY not only measures the number of life-years saved but it combines it with the “quality” of those years. It is both a quantitative and qualitative measurement. Studies have demonstrated high correlation between cost/ life-years and cost/QALY.⁸ For psoriasis, a chronic disease with low-mortality but high morbidity, QALY is a more appropriate measure than life-years saved and cost-utility analysis is likely the more appropriate outcome measure. However, the major disadvantage of using QALY is the subjectivity and variability of the qualitative component.

As mentioned above, most of the cost-effectiveness and cost-utility analyses currently published are performed through economic modeling. One of the advantages of

**TABLE 69-1—Currency Exchange Rates
(November/ 2009)⁴⁹**

	USD
FIM 1 (Finnish Markka)	0.23
€ 1 (Euro)	1.50
£ 1 (British Pound)	1.65
1 CHF (Swiss Franc)	0.99
1 CDN \$ (Canadian Dollar)	0.95

using models is that it allows head-to-head comparisons, even when there aren't previous clinical studies comparing two specific drugs.

METHODS

We searched the PubMed (U.S. National Library of Medicine), by using the Medical Subject Headings (MeSH) terms "psoriasis" and "cost-benefit analysis" or "cost-effectiveness". The abstracts were reviewed and among those, we selected the articles published in English that present a cost-effectiveness/utility analysis of psoriasis therapy. The currencies were all converted to US dollars (Table 69-1). We did not correct for inflation.

ECONOMIC EVALUATION MODELS

The information for cost-effectiveness analysis can be gathered directly from clinical trials, cohort studies, registries, and databases or through model building process. Economic models are a quantitative method organized to assess the value or utility of each option in the decision analysis process. Models have been increasingly used for cost-effectiveness analysis and they offer several advantages: they allow results from a shorter study to be extrapolated into longer time-horizons and clinical surrogates into final endpoints. Information from different studies can be included in the same model, allowing head-to-head comparisons between drugs that have not been compared in randomized-controlled trials (RCTs), for example. There are different decision-analytic models, such as Markov models, decision trees, and discrete event simulations. In all of them, some basic methodologic steps have to be taken. After defining the research question, a model structure has to be developed and into this structure, probabilities of each branch have to be assigned, as well as their utilities and costs. Besides the main structure (base-case result), different assumptions will be made to address uncertainty and test the robustness of the approach (sensitivity analysis)⁹.

Decision Trees

Decision trees are a simple tool that can be used in cost-effectiveness and decision analysis⁹. In these models, each

action leads to one or more consequences until final predetermined events occur at the end of the branching process. The events receive probabilities, based on the literature or expert knowledge, as well as utilities and costs. From each node (or branching point), different occurrences will have probabilities that add up to 100% of the probability of the previous occurrence. This type of model is very straightforward and easy to interpret and it is helpful to organize multiple phases of decisions. However, its simple design does not allow more complex courses, more similar to a real life situation to be evaluated.

Markov Model

A Markov model is a more refined and complex way of performing analytic modeling. It often is best applied to clinical situations with continuing risk, because it allows analysis of events that can recur over time as well as transient events. A Markov model is built by states, the Markov states. There are absorbing states (once patients reach this state, they cannot leave it), such as death. Temporary states are created for short-term events and patients usually do not return to them. At the end of the cycles, patients can change states. This model is built under the assumption that each patient is always in one of these states. Costs and utilities are assigned to each state. It is also taken into account the duration (number of cycles) that patients spend in non-death states. The analysis is performed within a limited time horizon^{9,10}.

In order to present the model, the most commonly used methods are cohort simulation and Monte Carlo simulation. In the first one, the model is performed on a hypothetical cohort of patients that transfer between states in each cycle. The analysis is then made on the number of patients in different states other than 'death' in each cycle. On the other hand, the Monte Carlo simulation includes a large number of individual patients that transfer randomly through the many states. Finally, the results for each patient in each cycle are summed, independently from their last state being an absorbing state or not. These two methods can lead to different results and, while the cohort simulation is straightforward, the Monte Carlo simulation imposes fewer limits to the model⁹.

Discrete Event Simulation

Discrete event simulation allows more flexible presentation of the data than the Markov model, at the cost of being more complex and time consuming. Events can happen at any time period after the previous event. The minimum time period has to be pre-specified, but the events can happen at different intervals. Each time an event occurs, the analysis is elicited. The results from the analysis that uses this method are similar to the results yielded by Markov model¹¹.

TOPICAL THERAPIES

Several studies have been reported that compare cost-effectiveness of topical treatments for mild to moderate psoriasis, especially with topical corticosteroids, calcipotriol and dithranol. These studies not only compare the performance of different drugs, but they also take into account the frequency and compliance of topical treatment that can be a challenge and reason for therapy failure for many patients. Costs of topical therapy are presented in Table 69-2 and vary widely based on generic versus branded status.

An economic analysis comparing topical tazarotene in the concentrations of 0.1 and 0.05%, topical corticosteroid (fluocinonide) and topical calcipotriol for the treatment of mild to moderate psoriasis used a decision-analytic tree from a meta-analysis carried out by the authors (Table 69-3). Success was defined as at least 50% improvement of psoriasis lesions in physician's assessment. Treatment failures led to treatment with secondary drug. Sensitivity analysis evaluated the impact of drug acquisition and medical-care costs, efficacy, and length of treatment in cost-effectiveness analysis. In this analysis, tazarotene 0.1% was found to be the most cost-effective treatment. The sensitivity analysis showed that for tazarotene 0.1% to lose the rank of most cost-effective topical therapy, its price and other associated costs would have to increase by 37% and 68%, respectively, and its efficacy decrease by 18%. It is unclear whether the prices used for the analysis are for branded or generic drugs.¹²

Calcipotriene was compared to different potency steroids in a retrospective analysis of a US claims database. Both total costs and medication costs per episode were calculated. The costs for calcipotriene (\$111/episode) were higher compared to the costs of ultra-high, high, mid, and

TABLE 69-3—Efficacy and Costs/Disease-Free Days (USD) of Topical Psoriasis Therapy¹²

	Success rates*	Relapse rates	Cost per disease-free day	Expected annual costs
Calcipotriol (4 week)	79.9%	41.4%	\$120.56	\$4219.65
Fluocinonide (4 weeks)	78.5%	44.9%	\$91.73	\$3394.08
Tazarotene 0.1% (12 weeks)	73.9%	37.4%	\$49.46	\$3412.96
Tazarotene 0.05% (12 weeks)	67.5%	35.1%	\$57.74	\$3464.61

*At least 50% improvement of psoriasis lesions.

low-potency corticosteroids (\$47 to \$75). However, when the total costs of therapy were taken into account, calcipotriene regimen costs were not significantly different from the costs of regimens using topical corticosteroids. The authors emphasize that costs per gram of topical drugs should not be used alone for comparison of psoriasis treatments.¹³

Ashcroft et al. compared calcipotriol twice a day versus dithranol short-contact regimen once a day. The decision trees used short and long-term horizons of 12 weeks and up to a year, respectively. Efficacy data and relapse rates were collected from previous head-to-head RCTs. The long-term model assumed that treatment failures would lead to use of the comparator drug. Costs of dithranol were based on Dithrocream® 2%. The costs are converted to US dollars in Table 69-4. Patient's perception of improvement in psoriasis was used as the endpoint for effectiveness. Sensitivity analysis with different efficacy and cost estimates (using data from other studies) was performed. The authors concluded that short-contact dithranol was the most cost-effective first line therapy because of reduced costs for acquisition of drug and more long-lasting remission of disease after treatment.¹⁴

A retrospective analysis of a Canadian clinical study evaluated the effect of adding calcipotriol cream

TABLE 69-2—Comparative Costs of Topical Therapies for Psoriasis²²

Topical medications	Wholesale price (USD/gram)	Monthly cost [§] (USD)
Fluocinolone acetonide (generic)	\$0.20	\$3.60
Betamethasone dipropionate (generic)	\$0.50	\$9.00
Clobetasol propionate (generic)	\$0.80	\$14.40
Calcipotriol (Dovonex®)	\$3.83	\$68.94
Betamethasone + Calcipotriol (Taclonex®)	\$7.45	\$134.10
Anthralin (Psoriatic®)	\$2.26	\$40.68
Tazarotene (Tazorac®)	\$4.25	\$76.50
LCD solution (Psorent®)	\$0.26	\$4.68

Adapted from Alora-Palli et al.²²

[§] Estimates based on use of 18 g/month (for 1% body surface area involvement)²⁸

TABLE 69-4—Efficacy and Costs Calculations (USD) of Calcipotriol Versus Dithranol¹⁴

Short term (12 weeks)			
Drug*	Success rates	Cost (USD)	Incremental cost [§]
Calcipotriol	60.8%	\$158.26	\$106.60
Dithranol	49.6%	\$51.67	—
Long term (1 year)			
Drug*	Relapse rates	Cost (USD)	Incremental cost [§]
Calcipotriol	80.6%	\$271.78	\$63.71
Dithranol	57.6%	\$208.07	—

*The frequency of use for calcipotriol and dithranol are, respectively, twice and once daily (short contact).

[§]Versus dithranol.

TABLE 69-5—Cost-effectiveness Analysis of Different Vehicles¹⁶

Group	Efficacy (decrease in PASI in 2 weeks)	Amount of medication/ % BSA treated (g)	Costs/ % BSA treated (USD)
Clobetasol Foam	41%	7.43	\$8.18
Clobetasol Cream/Solution	35%	10.16	\$7.05

(Daivonex®/ Dovonex®) once a day to a twice-weekly UVB regimen versus UVB three times a week combined with emollients. The former had lower than the latter over a 20-week period, representing a 3% drop in costs. However, the results did not hold after a sensitivity analysis with changes in costs of UVB therapy. This may be a good alternative for patients that are not able to comply with three sessions a week.¹⁵

One single-blinded study aimed to compare efficacy and cost-effectiveness of the same active ingredient, but administered in different vehicles. Patients with mild to moderate psoriasis presenting with both skin and scalp lesions were randomized into either clobetasol propionate (Olux®) foam 0.05% (skin and scalp) versus generic clobetasol cream 0.05% (skin) and solution 0.05% (scalp). This study showed that the foam was more effective in terms of absolute improvement in PASI, but not significantly different in terms of percent change in baseline PASI. Subjects reported relative less time for the foam application. The costs to treat 1% BSA were similar in both groups (Table 69-5). This study was limited by short treatment duration and small sample size.¹⁶

There are a few studies that evaluated cost-effectiveness of the dual-action compound of calcipotriol and betamethasone dipropionate versus each ingredient alone or both drugs in separate morning and night applications.^{17–20} They were based on evaluation of data from European centers. The first one was performed in Scotland¹⁷ and the second in Germany.¹⁸ These studies confirmed the findings of a similar analysis that compared three combinations of calcipotriol/betamethasone available versus morning and evening use of the active ingredients separately. Use of the combination was shown to be more cost-effective.¹⁹

One study compared the use of an ointment containing betamethasone dipropionate and calcipotriol (combination therapy - Daivobet®), once a day for 4 weeks, followed by calcipotriol (Dovonex®), only also once a day for 4 weeks versus tacalcitol (Apsor®, Curatoderm®, Bonalfa® and Vellutan®), only once a day for 8 weeks. Efficacy and cost-effectiveness were analyzed over 8 weeks. This evaluation was based on a randomized, double-blind study that included 501 subjects from 4 European centers. Sensitivity analysis was performed with and without subjects that withdrew from the study and assuming partial and complete treatment duration. The combination

TABLE 69-6—Cost-effectiveness Analysis of Combination Therapy with Calcipotriol/Betamethasone Dipropionate Versus Tacalcitol²⁰

	Efficacy (PASI \geq 75)* at 8 weeks	Total direct costs for psoriasis (USD) [§]	Cost/ successfully treated patient (USD)
Calcipotriol/betamethasone dipropionate (4 weeks) + Calcipotriol (4 weeks)	44.6%	\$ 161.54	\$ 362.38
Tacalcitol (8 weeks)	23.8%	\$ 170.51	\$ 716.15

* Last observation carried forward.

§ Costs included study drug, alternative treatment for psoriasis and other skin disorders and adverse events costs.

therapy was found to be more effective and cost-effective than tacalcitol alone for the treatment of plaque psoriasis (Table 69-6).²⁰

In the Scottish cost-utility analysis, calcipotriol/betamethasone dipropionate (Dovobet® - Leo Pharma - UK) was compared to other commonly prescribed therapies in England, such as calcipotriol once or twice a day, betamethasone dipropionate daily, or concurrent calcipotriol (morning) and betamethasone dipropionate (evening). An indirect comparison of randomized clinical trials was performed, using a Markov model with 12 1-month cycles. Sensitivity analyses evaluated several different assumptions, including different costs, response to phototherapy, amount of the topicals used, baseline utility, topical prescribed and utility while on the wait list for phototherapy, duration of the waiting list, PASI \geq 75 per treatment option, magnitude of utility gain associated with response and nonresponse, relapse rate of the comparators, and use of other potent steroid. They concluded that treatment with the two-compound calcipotriol/betamethasone dipropionate would lead to annual savings of approximately \$230.00 per patient compared to calcipotriol QD (1st choice), followed by steroids (2nd choice); and \$454.00, compared to use of the constituents separately (calcipotriol applied morning and betamethasone evening) (Table 69-7). It is unclear whether the cost calculations were based on generic or branded drugs.¹⁷

In the German study, a Markov model was also developed to evaluate the cost-effectiveness of the two-compound calcipotriol/betamethasone dipropionate (Daivobet® - LEO Pharma GmbH, Germany), followed by calcipotriol (Daivonex®), compared to the two individual agents used separately (Daivonex® and Diprosone®) (similar to the scheme in the previous study), as well as a comparison with tacalcitol (Curatoderm®). The most cost-effective approach was the two-compound calcipotriol/betamethasone dipropionate once daily (Table 69-8). This result did not change after allowing for variability of 10% in the efficacy of the compound product or assuming

TABLE 69-7—Cost-effectiveness Analysis of Combination Therapy with Calcipotriol/Betamethasone Dipropionate Versus Calcipotriol and Betamethasone Separately¹⁷

Drug	Frequency	Efficacy (PASI \geq 75)*	Costs/ 4 weeks (USD)	Estimated annual cost	QALY gained
Calcipotriol/betamethasone dipropionate	QD	50.3%	\$107.12	\$747.43	0.857
Calcipotriol	QD	13.8%	\$59.43	\$974.80	0.844
Calcipotriol	BID	23.0%	\$59.43	\$906.74	0.846
Betamethasone dipropionate	QD	36.2%	\$11.39	\$966.38	0.845
Calcipotriol + betamethasone dipropionate	Morning + evening	14.9%	\$46.29	\$1202.98	0.839

*Used as base-case. QD - once a day; BID - twice a day;

TABLE 69-8—Cost-effectiveness Analysis of Combination Therapy with Calcipotriol/Betamethasone Dipropionate Versus Tacalcitol Versus Calcipotriol and Betamethasone Separately¹⁸

	Frequency	DCD*/ patient/ total = 336 days	Estimated total costs/ 48 weeks (USD)	Costs/DCD* (USD)
Calcipotriol/betamethasone dipropionate	QD/ 4 weeks (followed by calcipotriol)	164.60	\$648.03	\$3.94
Tacalcitol	QD/8 weeks	156.19	\$979.91	\$6.28
Calcipotriol + betamethasone dipropionate	Morning + evening/ 8 weeks	144.19	\$733.18	\$5.08

* DCD - Disease controlled days - defined as clearance or significant improvement. QD - once a day

maximum compliance with the separate use of corticosteroid and calcipotriol.¹⁸

Topical therapies have also been compared to phototherapy in the treatment of moderate to severe psoriasis. An open-label, randomized study from the Netherlands compared short-contact dithranol, UVB phototherapy, and inpatient therapy with dithranol (Table 69-9). The duration of therapy was 12 weeks for UVB or short-contact dithranol and 8 weeks for inpatient therapy. Costs were calculated for the drug (it was not specified whether the generic or branded drug were used), physician and nurse's times, UVB unit, day-care unit, outpatient visits and inpatient costs. The authors concluded that short contact treatment is a cost-effective option for moderate to severe psoriasis when compared to inpatient treatment. However, UVB

phototherapy continues to be the first line therapy in these cases.²¹

A single-blinded study compared 15% LCD solution (Psorent[®]) versus 0.005% calcipotriol cream (Dovonex[®]) in the treatment of moderate psoriasis. Sixty subjects were randomized to one of the two treatment options for 12 weeks and were followed for 18 weeks total. Cost-effectiveness analyses were based on improvement of PASI and DLQI scores. Sensitivity analysis evaluated the impact of a different point of view having the patient as the payer with the respective prices of acquisition of OTC LCD solution and copayment for calcipotriol. LCD therapy proved to be more efficacious (higher improvement in PASI score) and less expensive than calcipotriol (Table 69-10). The effect of LCD solution was also more durable in the 6 weeks following therapy. Sensitivity analysis achieved similar conclusions.²²

TABLE 69-9—Cost-effectiveness Analysis of Dithranol Compared with UVB Phototherapy (Hartman)

	Success rates*	Costs/ treatment (USD)	Number of days of clearance
Short-contact dithranol	57%	2,465.27	160
UVB phototherapy	57%	1,889.89	136
Dithranol (inpatient therapy)	85%	11,576.72	211

* Decrease of at least 90% of BSA affected by psoriasis. UVB - ultraviolet B

PHOTOTHERAPY

A large noncontrolled study evaluating PUVA therapy was one of the first cost-effectiveness studies in psoriasis. It evaluated prospectively more than a thousand subjects. The number of days of hospitalization, concomitant therapies, and costs were evaluated during the year prior to PUVA and the year after the 10 months of phototherapy. Some patients remained on phototherapy during the subsequent year (continuers). PUVA not only improved psoriasis and

TABLE 69-10—Cost-effectiveness Analysis of Tar (LCD solution) Versus Calcipotriol²²

	Efficacy (% PASI improvement)	Cost of 1% improvement in PASI score	Efficacy (points of DLQI improvement)	Cost of 1 point improvement in DLQI score
Week 12				
LCD solution	58.2	\$0.92	5.1	\$10.50
Calcipotriol	36.5	\$35.42	3.5	\$360.04
Week 18				
LCD solution	52.5	\$1.01	6.9	\$7.70
Calcipotriol	22.2	\$58.11	2.8	\$450.05

LCD - Liquor Carbonis Detergents; DLQI - Dermatology Life Quality Index

What We Know: Topical Therapies

- Generic corticosteroids are relatively inexpensive options for topical treatment and have high short-term efficacy for mild to moderate psoriasis. They should be part of first-line therapy and could be applied alone or in combination with other topical or systemic therapies.
- Calcipotriol and Tar seem to be reasonable second-line options for mild psoriasis or could be combined with corticosteroids as first-line therapy for moderate disease. One study that compared these two drugs showed that tar (LCD solution) was more cost effective than calcipotriol.
- A few studies have shown that combination therapy of calcipotriol and corticosteroids works better than either active ingredient alone or their use in a morning and night regimen.
- Many factors have to be taken into account when prescribing topical treatments, such as vehicle used (e.g., foam is easier to be applied), cosmetic acceptability and convenience of application leading to better compliance.

TABLE 69-11—Overall Efficacy and Cost-effectiveness Analysis of PUVA²³

	Number of days of hospitalization (mean/year)	Cost of hospitalization per patient (USD)	Total costs of hospitalization + PUVA per patients (USD)
Pre-treatment year	5.1	\$1,550	\$1,550
Follow up year	1.2	\$360	\$970

decreased the need of concomitant therapy, it decreased the overall costs (Table 69-11).²³

Another uncontrolled clinical trial evaluated the impact of daily heliotherapy for 4 weeks in Spain for 46 Finnish patients. This evaluation compared the costs of therapy during the year prior to the heliotherapy course to the costs of heliotherapy and during the year afterwards. The average total direct costs decreased after the heliotherapy (Table 69-12). The cost reduction (22%) was not statistically significant though, because of large variability in

costs. Heliotherapy itself was expensive with estimated costs ranging from \$2309.24 to 4618.48. The authors point out that many patients in this study had mild disease and conclude that this therapy is effective and would be justified for patients with severe disease that require systemic drugs or hospitalization.²⁴

An economic analysis, using a decision tree built to reflect the AAD recommendations for rotational therapy for mild-to-moderate psoriasis, was performed to compare the impact of second-line therapy selections, particularly excimer laser. Costs for each therapy itself, office visits, and management of adverse events were included in the analysis. First-line therapy was topical corticosteroid plus calcipotriene. For nonresponders, second-line therapy included intralesional corticosteroid, excimer laser, PUVA, UVB phototherapy, tazarotene plus steroid and anthralin plus steroid. The estimated annual costs (US dollars - USD) per patient were \$2,340 in the model, including excimer laser and \$2,342 in the model excluding it. The conclusions

TABLE 69-12—Comparison of Costs Before and After Heliotherapy²⁴

	Costs/ time period (USD)
Pre-heliotherapy	\$1693.83/1 year
Heliotherapy in Spain	\$2837.83/4 wk
Post-heliotherapy	\$1316.27/1 year

TABLE 69-13—Comparison of Costs of Second-line Therapies for Psoriasis (USD)²⁵

Second line therapy	Cost of first line + one second-line therapy/ treatment free day	Cost of first line + one second-line therapy/ remission day	Estimated total annual costs	Cost/ treatment regimen
Intralesional corticosteroid	\$35.53	\$9.65	\$2,035	\$106.43
Excimer laser	\$41.61	\$10.73	\$2,335	\$909.36
UVB	\$56.56	\$13.10	\$2,653	\$1,412.64
PUVA	\$47.37	\$13.16	\$2,732	\$2,464.00
Anthralin + Corticosteroid	\$291.92	\$9.89	\$2,034	\$50.24
Tazarotene + Corsticosteroid	\$99.92	\$10.92	\$2,254	\$278.60

UVB - ultraviolet B; PUVA - psoralen combined with ultraviolet A

of this evaluation were that the 308-nm excimer laser was more cost-effective than other second-line options, such as UVB, PUVA, and topical therapies, in terms of the costs to attain a treatment-free day (Table 69-13). Adding the excimer laser to the rotational scheme resulted in improved clinical outcomes without adding costs.²⁵

A cost comparison between home ultraviolet B phototherapy versus systemic therapies for severe psoriasis has been performed using US data. The systemic drugs used in this payer perspective comparison were PUVA, methotrexate, acitretin, alefacept, efalizumab, and etanercept (efalizumab was not included in the results presented here, because it has been discontinued from the market). Doses are presented in Table 69-14. The time horizon used for this analysis was 30 years and, in addition to the head-to-head comparison of costs, a break-even analysis was performed to determine when the therapy with home UVB became more cost-effective than the other therapies.²⁶

The authors concluded that home UVB phototherapy had lower costs than the systemic therapies at 30 years horizon (Table 69-14). They also showed that, after a 2-year period, phototherapy had become the least expensive therapy for severe psoriasis. The initial costs of acquiring the home UVB phototherapy unit would be compensated by the very low costs in maintaining it and no requirement of follow-up tests.

The results from this analysis were straightforward and easy to interpret. However, the evaluation is limited to cost and does not include long-term effectiveness or safety issues. The authors acknowledge that no consistent data exists on efficacy of home UVB therapy. Sensitivity analyses were also not performed, so it was not tested whether different doses, for example, under different assumptions, would yield different results. The conclusions of this study would most likely not change, given such a striking difference in costs between the treatment options.

TABLE 69-14—Comparison of Home UVB Phototherapy with Systemic Therapy for Severe Psoriasis.²⁶

	Dose/Administration	Follow up tests	First year total costs (USD)	30-yr total costs
Home UVB	6 min EOD	None	2,345.04	7,085.27
PUVA	40 mg PO 30 sessions/yr	None	2,420.74	37,591.46
Methotrexate	15 mg PO/ week	CBC, LFTs (8x/year) + liver biopsy (every two years)	1,440.61	19,102.36
Acitretin	25 mg PO/day	Lipids and LFTs (4x/year)	4,900.43	75,112.69
Alefacept	15 mg IM 18 injections/yr	CD4 count (with each injection)	20,206.11	319,356.19
Etanercept	50 mg SC/week	PPD at initiation	16,596.60	257,683.89

UVB - ultraviolet B; EOD - every other day; PUVA - psoralen combined with ultraviolet A; PO - oral; SC - subcutaneous; CBC - complete blood count; LFTs - liver function tests; PPD - purified protein derivative

What We Know: Phototherapy

- The first cost-effectiveness studies in psoriasis evaluated phototherapy performance and showed that it reduced the days of hospitalization and consequently the costs of treatment.
- Phototherapy is not cost-effective for patients with mild disease that are responsive to topical therapies, but it is an excellent alternative for patients with moderate to severe disease as single or adjuvant therapy.
- The costs of the visits and the time devoted to the phototherapy sessions are the biggest disadvantages of this therapeutic approach.

SYSTEMIC THERAPY FOR PSORIASIS

A national survey estimated that 30% of patients with psoriasis require more than topical therapy.²⁷ For moderate to severe psoriasis, phototherapy, or systemic therapies (conventional and biologics) in monotherapy, or in combination with topical modalities are often used in clinical practice. Well-known conventional therapies (i.e., nonbiologics) include methotrexate (MTX), cyclosporine (CsA), and oral retinoids such as acitretin (Soriatane[®], Stiefel Laboratories Inc, Coral Gables, Florida). Biologics include alefacept (Amevive[®], Astellas Pharma US, Deerfield, Illinois), etanercept (Enbrel[®], Amgen, Thousand Oaks, California and Wyeth Pharmaceuticals Inc, Collegeville, Pennsylvania), infliximab (Remicade[®], Centocor Ortho Biotech, Malvern, Pennsylvania), adalimumab (Humira[®], Abbott Laboratories, Abbott Park, Illinois), ustekinumab (Stelara[®], Janssen-Ortho Inc, Toronto Ontario) and efalizumab (Raptiva[®], Genentech, South San Francisco, California). Efalizumab was withdrawn from the market in 2009 for its association with progressive multifocal leukoencephalopathy and will, therefore, not be further discussed.

The cost of systemic psoriasis therapies is highly variable (Table 69-15) with conventional therapies (approximately \$63.50 to \$750 per month USD) costing far less than biologics (approximately \$1100 to \$1800 per month USD).²⁸ However, laboratory monitoring of systemic therapies need to be included in cost calculations and change the relative costs somewhat (Table 69-16).

Nonbiologics

Methotrexate (MTX) has long been considered the “gold-standard” for moderate to severe psoriasis treatment over the past 40 years²⁹ and is one of the most commonly prescribed systemic treatments for psoriasis. A chemotherapy agent in higher doses, MTX, likely acts as an immunosuppressant in lower doses. Efficacy of MTX for psoriasis ranges from 43-82%.²⁸ MTX requires monthly laboratory work to monitor bone marrow and liver function as well as a surveillance liver biopsy to rule out cirrhosis for each cumulative dose of 1500 mg (i.e., approximately every 2 years of continuous therapy). MTX is available in tablet or an injectable liquid (for intramuscular IM, subcutaneous SC or intravenous IV administration). The liquid form is less expensive than the tablet (Table 69-17) and can also be taken orally.²⁸

Using a visual analog scale survey comparing visual clinical improvement in mild, moderate, and severe psoriasis patients on oral (tablet or liquid) MTX versus Goeckerman therapy, dermatology faculty (staff and residents), psoriasis patients, and a sample of people without psoriasis nor their treating physicians, Chen et al.³⁰ concluded that Goeckerman therapy was less cost-effective than liquid MTX in severe psoriasis patients over a 52-week extrapolated model. Sensitivity analysis assumed that the best case

with MTX was 82% clearance (for moderate to severe), 18% clearance (for mild) while the worst case with MTX was 43% clearance and 57% with no improvement, while the best case with Goeckerman therapy was 100% clearance and worst case was 90% clearance (for moderate to severe) and 100% clearance (for mild). These conclusions were challenged by Lim et al.³¹ by highlighting issues related to actual costs of physician visits on MTX, safety issues with patients extracting their own doses of liquid MTX from 25 mg/mL vials and typically short remission periods from MTX (2-3 months) versus Goeckerman (20-22 months).³²

Cyclosporin (CsA) was developed as an immunosuppressant agent used in transplant patients. CsA tends to be highly effective and rapid acting for PsO, but is associated with numerous adverse effects including hypertension, dyslipidemia, and nephrotoxicity; and therefore requires monthly serum creatinine and blood pressure monitoring. The US Food and Drug Administration (FDA) recommends that continuous CsA therapy should not exceed 1 year, while an international consensus statement on the use of CsA for psoriasis suggests limiting CsA to two years.³³

Hakkaart-van Roijen et al. in a multicenter, nonblinded international clinical trial ($n = 212$) conducted in parallel to the Psoriasis Intermittent Short Course Efficacy of Sandimmun Neoral[®] trial (PISCES)³⁴ compared the effects of tapered dosages versus abrupt discontinuation of CsA over a 1 year period for patients with chronic plaque-type psoriasis. These patients were treated with CsA until clearance (at least 90% BSA reduction in BSA) or up to 12 weeks, then either discontinued or tapered from therapy; retreatment was instituted for relapse (greater than 75% BSA). Outcome measures for systemic therapy free days (STFD) and cost-effectiveness ratio (ICER) found that a slow CsA taper was more cost-effective yielding an additional 32 days of STFD and reduction in cost per patient by \$US258 (ICER -8.1).³⁵

Ellis et al. used a computer decision analytic model with Markov processes of 1000 simulated patients with moderate ($n = 800$) and severe ($n = 200$) psoriasis not responsive to topical therapy. Patients were randomly assigned a treatment regime of either primarily MTX 10 to 20 mg/week or CsA 3 to 3.5 mg/kg/day with methotrexate 10 to 20 mg/week (CsA/MTX) in 1-year rotational cycles. Data was used to determine 10-year costs of therapy. Their analysis determined that MTX strategy cost \$33,000 USD over 10 years with approximately 2 years of clearance (i.e., \$4,100 per clear year), while CsA/MTX rotational strategy cost \$38,000 USD over 10 years with approximately 4 years of clearance (\$2,700 USD per clear year), thereby suggesting a greater cost-effectiveness of rotational therapy.³⁶

Oral retinoids such as isotretinoin and acitretin are also used in psoriasis. In particular, acitretin can be effective for erythrodermic and pustular psoriasis,³⁷ but less than one-third of plaque-type psoriasis are responsive. Oral retinoids are associated with many unpleasant adverse effects, namely xerosis, cheilitis, musculoskeletal symptoms, in addition to

TABLE 69-15—Approximate Costs Calculations Used for Systemic Psoriasis Therapy.^{28,50}

Medication (administration route)	Dosage (annual doses)	Per Unit Medication Cost USD ^{28,40}	Cost Calculations	Approximate Annual Cost USD
Nonbiologics				
Methotrexate (PO, SC, IM)	10 mg/week (52)	31.99 for 2.5 mg tabs (x30), 24.99 for 10 mL (25 mg/ml)	R3 office visits ×8, lab work ×8, liver biopsy	\$1200-\$1800
	15 mg/week (52)	90.75 (tablet)* 6.00 (liquid)	R3 office visits ×8, lab work ×8, liver biopsy	\$1400-\$2300
	20 mg/week (52)	31.99 for 2.5 mg tabs (x30), 24.99 for 10 ml (25 mg/ml)	R3 office visits ×8, lab work ×8, liver biopsy	\$1700-\$2800
Cyclosporin (PO)	3 mg/kg/day (365)	538.00 for 100 mg × 60 tabs (based on 70 kg)	R3 office visits ×8, lab work ×8	\$5800-6500
	5 mg/kg/day (365)	507.15 - 602.70* (based on 70 kg)	R3 office visits ×8, lab work ×8	\$9000-10100
Acitretin (PO)	25 mg/day (365)	347.40 - 406.62*	R3 office visits ×8, lab work ×4	\$6000
Biologics				
Alefacept (route: IM, IV)	7.5 mg IV (18)	2155.83* 995 per 15 mg (2 vials)	R3 office visits × 8, CD4×18, infusions	\$16,600
	15 mg IM (18)	2155.83* 995 per 15 mg (2 vials)	R3 office visits ×8, CD4×18, injections	\$19,500
Etanercept (route: SC)	25 mg twice weekly (128)	1132.99 - 1306.00* (839.85 per 4 dose injection kit)	R3 office visits ×8, PPD×1	\$17,700
	50 mg twice weekly (128)	1646.16 - 1729.09 per 4 dose injection kit	R3 office visits ×8, PPD×1	\$34,800
Infliximab (route: IV)	5 mg/kg week 0, 2, 6, then every 8 weeks (8)	671.82 per 100 mg (1 vial)	R3 office visits ×6, PPD×1, CXRx1, infusions	\$17,700
	10 mg/kg week 0, 2, 6, then every 8 weeks (8)	671.82 per 100 mg (1 vial)	R3 office visits ×6, PPD×1, CXRx1, infusions	\$34,300
Adalimumab (route: SC)	80 mg at week 0, then 40 mg every other week (18)	719.85 per 40 mg syringe, or 1715.74 - 1745.19 for 40 mg injections × 2	R3 office visits ×8, PPD×1	\$17,700
	80 mg at week 0, then 40 mg weekly (52)	719.85 per 40 mg syringe, or 1715.74 - 1745.19 for 40 mg injections × 2	R3 office visits ×8, PPD×1	\$34,800
Ustekinumab (route: SC)	45 mg week 0 and 4, then every 12 weeks (6)	N/A	R3 office visits ×6, PPD×1	\$23,000 (approx)
	90 mg week 0 and 4, then every 12 weeks (6)	N/A	R3 office visits ×6, PPD×1	\$46,000 (approx)

Legend: IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous

CXR = chest x-ray, PPD = purified protein derived tuberculin at treatment initiation. Methotrexate lab work = Complete blood count, liver enzymes (AST, ALT, alkaline phosphatase and bilirubin) and creatinine prior to therapy, then monthly thereafter. Cyclosporin lab work: complete blood count, complete metabolic panel, creatinine, lipid panel (total cholesterol, triglycerides, LDL and HDL), cyclosporine levels and blood pressure monthly. Acitretin lab work: Complete blood count, liver function (AST, ALT, alkaline phosphatase and bilirubin), lipid panel prior to therapy, then monthly for the first 3-6 months, then every 3 months thereafter.

Monthly costs of medication were determined by Pearce et al. (2004) from the average wholesale price (AWP) listed in the 2003 Drugs Topics Red Book* and www.drugstore.com internet pharmacy.

teratogenicity in women of childbearing age. Laboratory work is required for monitoring liver function and lipid profiles. Estimated annual cost of acitretin 25 mg daily is \$6000.²⁸

Biologics

Five FDA-approved biologic agents for the treatment of psoriasis etanercept (Enbrel[®]), infliximab (Remicade[®]),

alefacept (Amevive[®]), and adalimumab (Humira[®]) and ustekinumab (Stelara[®]) will be discussed.

PASI 75 Comparisons

Two systemic reviews expressed cost-effectiveness in the context of attaining PASI 75 (Tables 69-18 & 69-19). Greiner & Braathen (2009) evaluated cost-effectiveness of

TABLE 69-16—Costs Associated with Monitoring Laboratory Investigations^{26,36,40}

Investigation	CPT Code	Cost (USD)
Complete blood count and differential	85025	\$23(10-50)
Creatinine	82565	\$100(50-250)
Chest x-ray	71020	36
CD4 count	86360	89
Infliximab infusion	90765, 90766	78 per first hour, then \$26 per additional hour
PPD	86580	10 per test
R3 physician office visit	99213	53-75
Percutaneous liver biopsy	47000	\$750(300-1300)

Legend: IM = intramuscular; IV = intravenous; PO = oral; SC = subcutaneous
 CXR = chest x-ray, PPD = purified protein derived tuberculin at treatment initiation. Methotrexate lab work = Complete blood count, liver enzymes (AST, ALT, alkaline phosphatase and bilirubin) and creatinine prior to therapy, then monthly thereafter. Cyclosporin lab work: complete blood count, complete metabolic panel, creatinine, lipid panel (total cholesterol, triglycerides, LDL and HDL), cyclosporine levels and blood pressure monthly. Acitretin lab work: Complete blood count, liver function (AST, ALT, alkaline phosphatase and bilirubin), lipid panel prior to therapy, then monthly for the first 3-6 months, then every 3 months thereafter.

biologics used in Switzerland, adjusted to Swiss prices and tariffs in 2006. These authors determined ICER in patients achieving PASI 50, 75, or 90, at weeks 12 with responders (PASI >50) continuing to 24 weeks; analytic models were used to determine ICER at 36 weeks. Placebo-adjusted values for infliximab 5 mg/kg demonstrated the highest efficacy (i.e., 77.8% and 78.4% with PASI 75 at weeks 12

and 24 respectively), with the lowest ICER \$29,730 (from a 36-week extrapolated model), followed by adalimumab (i.e., 56.0% and 61.5% with PASI 75 at week 12 and 24 respectively, ICER \$29,160) and etanercept (i.e., 46.4% and 50.9% with PASI 75 at week 12 and 24 respectively, ICER \$35,286), while alefacept comparatively had the lowest efficacy (i.e., 16.0% and 20.0% with PASI 75 at week 12 and 24 weeks respectively), with the highest ICER \$48,606 (see Table 69-18).³⁸

Poulin et al., (2009) pooled data from randomized-controlled trials studying the use of biologics for chronic plaque psoriasis published through December 2008 (Table 69-19). Their analysis determined the number needed to treat and the estimated cost to achieve PASI 75, based on product monograph recommended doses for the first year of therapy. Annual treatment cost ranged from \$18,752 to 35,577 USD per patient. From their analysis, the most cost effective agent to achieve PASI 75 at 12 weeks and 1 year respectively was adalimumab (\$7,879, \$27,578), followed by ustekinumab (\$11,859, \$35,577) and infliximab (\$14,290, \$38,106). The least cost-effective was alefacept (\$67,150, \$135,020).³⁹

PASI 75 & DLQI Comparison

Nelson et al., (2008) performed a meta-analysis of pooled data from randomized-controlled trials from January 1, 2003 and January 1, 2007, to compare the cost-effectiveness of biologics to achieve a minimally important difference Dermatology Quality of Life Index (DLQI-MID) and PASI 75 over a 12-week treatment course (Table 69-20). Over the 12-week treatment period, the most cost-effective biologics in attaining DLQI-MID improvement were etanercept 25 mg weekly (\$2,250 USD) followed by infliximab 3 mg/kg (\$3,508), adalimumab 40 mg every other week (\$3,511).⁴⁰

TABLE 69-17—Comparison of Methotrexate (Oral and Liquid) Versus Goeckerman Therapy³⁰

Treatment	Psoriasis severity	Estimated Annual Cost (USD)	ICER versus supportive care (USD) based on dermatology faculty ratings	ICER versus supportive care (USD) based on psoriasis patients ratings
MTX (tablet)	Mild	1,836	26,515	15,305
	Moderate	1,861	12,899	8,872
	Severe	1,898	8,147	8,111
MTX (liquid)	Mild	2,366	20,577	11,878
	Moderate	2,744	8,748	6,017
	Severe	3,311	4,670	4,649
Goeckerman therapy	Mild	5,104	34,314	19,807
	Moderate	5,104	17,941	12,136
	Severe	5,104	10,146	9,754
No treatment	—	0	—	—

MTX = methotrexate

TABLE 69-18—ICER Per PASI 75 for Biologics Using a 36-Week Model (2006 Costs) in Switzerland³⁸

Biologic Medication	Dose	PASI 75 (% patients) Week 12	PASI 75 (% patients) Week 24	Cost per patient to attain PASI 75 36 week model (USD)
Adalimumab	80 mg SC week 0, then 40 mg EOW	56.0	61.5	29,160
Alefacept	15 mg IM weekly	16.0	20.0	48,606
Etanercept	50 mg SC twice weekly	46.4	50.9	35,286
Infliximab	5 mg/kg IV	77.8	78.4	29,730

ICER = incremental cost-effectiveness ratio; PASI 75 = 75% improvement from baseline. EOW - every other week; IM - intramuscular; SC - subcutaneous

TABLE 69-19—Estimated Costs of Biologics to Achieve PASI75 Over 12 Weeks and 1 Year³⁹

Biologic Medication	Dose	Annual Cost (USD)	NNT	PASI75 (% patients)	Cost per patient to achieve PASI 75 - 12 weeks (USD)	Cost per patient to achieve PASI 75 - 1 year (USD)
Adalimumab	80 mg week 0, then 40 mg QOW with week 1	18,752 (28 doses)	1.6	68	7,879	27,578
Alefacept	15 mg week 0 to 12, then repeat as needed	14,177 (12 doses) 29,976 (24 doses)	5.6	21	67,510	135,020
Etanercept	50 mg 2×/wk week 0 to 12, then 50 mg weekly	23,313.92 (12 × 100 mg, 40 × 50 mg)	2.3	49	16,877	45,005
Infliximab	5 mg/kg (based on 80 to 90 kg)	30,080.00 to 37,600.00 (8 × 400 mg or 500 mg)	1.3	84	14,290	38,106
Ustekinumab	45 mg week 0 and 4, then every 12 weeks	25,200 (6 doses)	1.6	67	11,859	35,577

NNT = number needed to treat; PASI 75 = 75% improvement from baseline.

TABLE 69-20—Cost to Attain DLQI-MID and PASI-75 Over a 12-Week Treatment Course⁴⁰

Biologic Medication	Dose	Cost (USD)	Mean DLQI change	Cost per patient to achieve DLQI MID (USD)	PASI75 (% patients)	Cost per patient to achieve PASI 75 (USD)
Etanercept	25 mg 1×/wk	2,381.52	5.8	2,250	14.4	19,111
	25 mg 2×/wk	4,541.04	7	3,599	33.4	14,254
	50 mg 2×/wk	8,860.32	7.5	6,645	49.2	18,738
Placebo	N/A	222	1	—	3.1	—
Infliximab	3 mg/kg (3 infusions)	6,599.12	9	3,508	70.6	8,797
	5 mg/kg (3 infusions)	8,547.16	9.7	4,322	79.1	10,422
	10 mg/kg (3 infusions)	16,499.32	N/A	N/A	N/A	N/A
Placebo	N/A	595	0.5	—	2.8	—
Adalimumab	40 mg every other week	5,980.8	9.5	3,511	53.3	11,657
	40 mg weekly	10,299.9	10.2	5,662	80	13,243
Placebo	N/A	222	1.3	—	3.9	—
Alefacept	15 mg weekly	13,644	4.9	27,136	21.1	74,625
Placebo	N/A	1,704	2.7	—	5	—

DLQI: Dermatology Quality of Life Index; DLQI-MID: Dermatology Quality of Life Index minimally important improvement; PASI: Psoriasis Assessment Severity Index; PASI 75: 75% improvement from baseline; N/A: not applicable.

In comparison, the most cost-effective biologic agents to achieve PASI 75 in the most patients were infliximab 3 mg/kg (\$8,797 USD, 70.6%), followed by infliximab 5 mg/kg (\$10,422, 79.1%) and adalimumab 40 mg every other week (\$11,657, 53.3%). Estimated annual cost of infliximab administration (based on three infusions per year) ranges from \$6,559.12 (3 mg/kg/infusion) to \$8,547.16 (5 mg/kg/infusion) to \$16,499 (10 mg/kg/infusion). A cost-effectiveness meta-analysis comparing 3 mg/kg and 5 mg/kg versus placebo over a 12-week period reported mean DLQI improvement of 9.0 and 9.7 (versus 0.5 with placebo) with 70.6% and 79.1% achieving PASI 75 respectively. Cost per patient to reach PASI 75 was \$8,797 and \$10,422 respectively versus placebo.⁴⁰ The least cost-effective biologic to achieve DLQI-MID and PASI 75 was alefacept 15 mg IM weekly and over a 12-week period mean DLQI improvement of 4.9 (versus 2.7 with placebo), with 21% achieving PASI 75. Cost per patient on alefacept to reach PASI 75 is \$74,625.⁴⁰

PASI 75 & Quality Adjusted Life Years (QALY) Comparison

Sitzo et al., (2008) analyzed 22 randomized controlled trials conducted over a 12-16 week period comparing biologics (adalimumab, etanercept and infliximab) to nonbiologic systemic agents (MTX, CsA), and supportive care in patients with moderate to severe psoriasis using PASI 75 and quality-adjusted life years (QALY) with cost-effectiveness ratios based upon QALY (Table 69-21).⁴¹ Compared to supportive care (baseline), both MTX (ICER -\$49,045) and CsA (ICER -\$41,424) appeared to be most

cost-effective, but were noted to require monitoring for systemic toxicity. While infliximab had the highest incremental QALY (0.18) compared to supportive care, adalimumab was most cost-effective (ICER \$49,442 per QALY), followed in sequence by etanercept (ICER \$60,979 per QALY) and infliximab (ICER \$69,219 per QALY).⁴¹

QALY COMPARISON

Heinen-Kammerer et al., (2007) pooled data from three clinical trials to compare the cost-effectiveness of etanercept 25 mg twice weekly to nonsystemic therapy for moderate to severe plaque-type psoriasis using QALY gained extrapolated over 10-years (Table 69-22).⁴² In their model, patients were started on etanercept for 12 weeks. Responders (PASI \geq 75) were discontinued active treatment until PASI decreased by 50%. Partial responders (PASI <75) continued with treatment for another 12 weeks and those that did not reach PASI 75 were considered nonresponders. All nonresponders (from initial 12 week period) and partial responders that did not respond to a second 12-week course of etanercept did not receive further treatment. Estimated cost for medication and physician's fees for etanercept and basal therapy per 4-week cycle were \$2,577.15 and \$37.24 respectively. These authors reported that increased PsO severity is associated with decreased cost per QALY with increased PsO severity from \$68,341 (PASI & DLQI >10) to \$27,273 (PASI & DLQI >20). Furthermore, for the most severe (PASI and DLQI >20), the ICER decreased with increasing age: ICER \$27,047 (age >20), \$23,117 (age >40) and \$9,325 (age >60). Sensitivity analysis for PASI and DLQI >20 with basal treatment consisting of

TABLE 69-21—Comparison of Cost-effectiveness of Nonbiologic and Biologic Agents to Supportive Care Using QALY⁴¹

Medication	Dose	Cost versus supportive care (USD)	Mean QALY	PASI75 (%patients)	ICER per QALY versus supportive care (USD)	ICER per QALY versus biologics (USD)
Methotrexate	15-25 mg/week	-6,335	0.13	37	-49,045	N/A
Cyclosporine	3 mg/kg/day (80 kg person)	-3,275	0.08	34	-41,424	N/A
Adalimumab	40 mg every other week	8,229	0.16	67	50,329	50,329
Etanercept	25 mg 2x/wk (intermittent)	6,780	0.11	38	61,447	Extended domination
Etanercept	50 mg 2x/wk (intermittent)	7,744	0.12	52	63,217	Extended domination
Etanercept	continuous	8,336	0.13	N/A	62,093	Dominated
Infliximab	5 mg/kg (80 kg person)	12,749	0.18	81	70,030	243,759
Supportive Therapy	-	0	0	5	-	N/A

Extended domination – ICER greater than another drug, but either the costs or QALY are more favorable. QALY - quality-adjusted life year; ICER - incremental cost-effectiveness ratio; PASI 75 - 75% reduction in Psoriasis Area and Severity Index

TABLE 69-22—Comparison of Intermittent Etanercept 25 mg Twice Weekly to Basal Therapy Over a 4-Week Cycle Using Quality-Adjusted Life Years (QALY) in Germany

Treatment	PASI & DLQI (n)	Cost per 4-week cycle* USD	Cost over 10 years USD	QALY	Cost per QALY USD
Etanercept	>10	2,577.15	71,440	0.96	68,341
Basal therapy	(n=479)	37.24	61,662	0.82	—
Etanercept	>15	2,577.15	72,028	1.34	48,161
Basal therapy	(n=192)	37.24	61,662	1.13	4.66
Etanercept	>20	2,577.15	82,617	1.74	27,273
Basal therapy	(n=87)	37.24	72,656	1.37	4.66

*Cost includes medication and physician fees.

QALY = quality adjusted life years, PASI = psoriasis adjustment severity index; n = number of patients.

systemic therapies (cost \$180/cycle), and 30% reduction in hospitalization risk from etanercept therapy reported ICER values to be \$23,808 for basal therapy, \$24,525 for intermittent etanercept and \$36,109 for hospital stay. These authors concluded that intermittent etanercept 25 mg twice weekly is most cost-effective for severe (and moderate) psoriasis, particularly in older patients.⁴²

Woolacott (2006) in a systemic review of etanercept and efalizumab for the treatment of psoriasis performed several cost comparison analyses (Table 69-23). For any baseline DLQI treated with etanercept twice weekly compared to supportive therapy (without hospitalization), biologic therapy would not be cost-effective unless the cost-effectiveness threshold approaches ICER \$115,365 per QALY gained. Comparing patients with any baseline DLQI versus those with low fourth quartile DLQI only on supportive care (without hospitalization), the cost for treatment was \$109,931 (any DLQI) versus \$57,409 (fourth quartile DLQI) for etanercept 25 mg (intermittent), \$137,215 versus \$71,656 for etanercept 25 mg (continuous), and \$199,177 versus \$103,998 for etanercept 50 mg (intermittent).⁴³ The first scenario using only patients with baseline DLQI in the fourth quartile determined the threshold of cost-effectiveness would be ICER \$57,682,

thereby favoring supportive care (without hospitalization) below this threshold and biologics entering the sequence as intermittent etanercept 25 mg followed by continuous etanercept 25 mg above this threshold. The second scenario included any baseline DLQI where all nonresponsive patients would undergo a 21-day (adjusted \$409/day from NHS Reference Costs 2003 and National Tariff 2004) inpatient hospitalization per year; etanercept 25 mg (intermittent) entered in the treatment sequence with ICER \$49,442 followed by continuous etanercept 25 mg with ICER \$82,404. The third scenario accounted for patients in the fourth quartile DLQI and assumed nonresponsive patients undergoing a 21-day inpatient hospitalization; etanercept 25 mg (intermittent) entered the sequence with ICER \$32,961 followed by continuous etanercept 25 mg with ICER \$32,961. The fourth scenario included any baseline DLQI on several systemic therapies and supportive therapy with nonresponders requiring 21 days per year of inpatient hospitalization; biologics enter the treatment sequence with etanercept 25 mg (intermittent, ICER \$48,537), etanercept 25 mg (continuous, \$75,852), infliximab (\$85,284) etanercept 50 mg (intermittent, \$137,906) only after failure of methotrexate and cyclosporine.⁴³ When PASI scores from all treatments were compared, the most

TABLE 69-23—Cost-effectiveness of Systemic Therapies for Psoriasis Over 12-Weeks Using Quality-Adjusted Life Years in the United Kingdom (QALY)⁴³

Medication	Dosage	Incremental Cost (USD)	QALY improvement	Incremental Cost (USD)	ICER/QALY versus supportive care (USD)
Etanercept (intermittent)	25 mg 2x/wk for 12 weeks	5,628	0.116	5,628	48,537
Etanercept (continuous)	25 mg 2x/wk for 12 weeks	8,796	0.116	8,796	75,852
Etanercept (intermittent)	50 mg 2x/wk for 12 weeks	16,906	0.123	16,906	137,576
Infliximab	3-5 mg/wk × 3 doses in first 6 weeks, then every 8 weeks	11,401	0.134	11,401	85,284
Methotrexate	Weekly	-6,960	0.126	-6,960	dominates
Cyclosporin	1-2 mg/kg Weekly	-745	0.122	-745	dominates
Supportive care, hospitalization	N/A	-	-	-	-

QALY = quality adjusted life years. ICER - incremental cost-effectiveness ratio

TABLE 69-24—Cost-effectiveness of Licensed Regimes of Etanercept Over 12 Weeks (Extrapolated to 10 Years) for PASI and DLQI > 10 Psoriatic Patients Using Quality-Adjusted Life Years (QALY) in the United Kingdom⁴⁴

Medication	Dosage	Cost (USD/10 years)	Incremental Cost (USD/10yrs)	QALY improvement	ICER versus no systemic therapy (USD)
Etanercept	25 mg 2×/wk, then 25 mg (intermittent)	73,924	4,730	0.67	7,082
Etanercept	50 mg 2×/wk, then 25 mg (intermittent)	78,427	9,234	0.9	10,246
No systemic therapy	—	69,194	—	—	—

efficacious psoriasis treatment was infliximab, followed by methotrexate and cyclosporine, then etanercept 50 mg (twice weekly), then etanercept 25 mg (twice weekly).⁴³

Lloyd et al., (2009) used an economic model to determine the incremental cost per QALY gained for etanercept 50 mg twice weekly in chronic plaque-type psoriasis patients with DLQI and PASI ≥ 10 ($n=671$) who were not candidates for other forms of systemic therapy.⁴⁴ The study pool data from three randomized placebo-controlled studies using licensed etanercept treatment regimes for at least 12-week duration (Table 69-24). In their model, patients were started on either etanercept 25 mg or 50 mg twice weekly for 12 weeks. Responders (PASI ≥ 75) discontinued active treatment until response was lost. Partial responders (PASI < 75) continued with their respective treatment for another 12 weeks and those that did not reach PASI 75 did not receive further treatment. All patients that did not reach PASI 50 from the initial 12-week period were discontinued from the study. These authors found that incremental cost per QALY were \$7,082 and 10,246 for etanercept 25 mg and 50 mg biweekly, followed by intermittent 25 mg biweekly for relapses. Sensitivity analysis with etanercept 50 mg twice weekly compared to no systemic therapy found that incremental cost per QALY with PASI > 20 (\$8509) and

DLQI > 20 (\$7579) made this treatment regime a cost-effective option for severe psoriasis.⁴⁴

DISCUSSION

Cost-effectiveness analysis is a tool that can be used to evaluate the therapeutic and economic trade-offs for an intervention. In this era of cost containment, the efficacy, utility, safety, and cost of medications need to be assessed in an integrated way in order to prioritize how to choose therapies on a societal level. Unfortunately, even the most comprehensive models likely miss or are forced to omit some relevant details. Moreover, information gathered from cost-effectiveness analyses based on data from randomized-controlled trials may not reflect ‘real world’ settings, whereas other factors affect adherence, efficacy, and cost. External validation may be one way to solve this problem,⁴⁵ but to date, most evaluations are based on models, rather than prospective collection of cost data. Lastly, and perhaps most importantly, in an individual patient, risk factors, preferences, quality of life, economic productivity, and coping, may be relevant parts of therapeutic decision-making. These considerations can only be evaluated and addressed within the individual physician-patient construct.

What We Know: Systemic Therapies

- Conventional systemic agents for psoriasis include methotrexate, cyclosporin, and acitretin. Depending on the dosage, the annual costs of these agents are relatively low, ranging from approximately \$1,200 to 2,800 USD for methotrexate, \$5,800 to \$10,100 USD for cyclosporin and \$6,000 for acitretin.
- Biologic agents for chronic plaque psoriasis include infliximab, adalimumab, and etanercept (anti-tumor necrosis factor agents), alefacept (inhibitor of CD4 and CD8 T-cells), as well as ustekinumab (interleukin 12 and 23 antagonist). Furthermore, antitumor necrosis factor agents are also effective for psoriatic arthritis. Annual costs for these agents range from \$15,000 to \$38,000 USD.
- A cost-effective clinical approach to the management of chronic plaque psoriasis would start with a conventional systemic agent such as methotrexate or cyclosporin. Failure of a therapeutic trial or contraindications to these agents would be followed by management with biologic agents.
- Based on the available cost-effectiveness comparisons of biologic agents for chronic plaque psoriasis, it would be reasonable to start a patient on adalimumab 40 mg every other week or infliximab 5 mg/kg every 8 weeks or ustekinumab 45 mg every 12 weeks. Alefacept was the least cost-effective agent demonstrated in cost-effectiveness comparisons.
- Biologic agents, particularly antitumor necrosis factor-alpha agents (e.g., adalimumab, infliximab, and etanercept) should be considered in patients with psoriasis and concomitant psoriatic arthritis.

The majority of psoriasis patients have mild to moderate disease and can be potentially treated with topical therapy.⁴⁶ While there are some studies comparing specific therapies this area is problematic for analysis across studies because efficacy, the definition of success, and cost-effectiveness have not been measured uniformly. In general, while generic formulations of topical medications are substantially less expensive than the branded alternatives, some of the novel ingredients or better formulations of branded products performed similarly in some cost effectiveness analyses because of improved efficacy, adherence, or both. Of note, for patients with large body surface areas affected by psoriasis (<10%), systemic medications can be more cost-effective when compared to some of the more expensive branded medications.

For UV and systemic therapies, older studies of cost-effectiveness are somewhat non-uniform, but more recent studies have employed similar methodologies and scoring systems allowing for more comprehensive analyses across studies. In general, while biologic agents have the potential to achieve high PASI scores, the cost of the medication itself, is more expensive than topical or conventional systemic therapies. However, because of their substantial efficacy, the incremental cost of biologics per QALY generally fall within acceptable economic ranges. Additionally for some patients, there would be a gain in treating concomitant psoriatic arthritis: around 30% of moderate to severe psoriasis patients are also afflicted by psoriatic arthritis⁴, and the combination of the effects on both conditions should be considered when performing economic analysis in this population.⁴⁷

From the studies available for analysis, it appears that a rational clinical and cost-effective approach would be to start with UV or conventional systemic therapies (i.e., MTX, CsA or acitretin) where medically appropriate, and failing these medications, biologics should be considered. UV therapy can be very cost-effective, but is currently discouraged in the United States based on high copays set by private insurers, which ironically, may not be in their best interest. Based on cost-effectiveness studies available to date, biologics should be considered in the following sequence: adalimumab, infliximab or ustekinumab, then etanercept and finally alefacept. We were only able to locate one cost-effectiveness study on ustekinumab³⁹ as this is a relatively new addition to the biologic market. Furthermore, it is unclear if ustekinumab offers any benefit for psoriatic arthritis, unlike its predecessor anti tumor necrosis factor-alpha agents (i.e., infliximab, adalimumab, and etanercept).

Of note, many studies presented conflicts of interest. Some of them were funded by pharmaceutical companies that manufacture the drugs being analyzed or their employees were directly involved in the design and analysis process.

One additional problem in applying these economic analyses is that in clinical practice, multiple medications

are often used simultaneously to augment effectiveness or allow for treatment of specific body regions. On face, this approach may increase cost,⁴⁸ but if it allows decreased dosing of other more expensive medications such as a biologic or expensive systemic therapy, it may be more cost-effective.

Lastly, a clear limitation of current cost-effectiveness studies is a limited time horizon. Psoriasis is a chronic disease that lasts decades in some patients and most efficacy studies include only short-term data.

In summary, cost-effectiveness analyses are an important integrated way to inform therapeutic decision-making, but do depend on the assumptions that underlie their models. Progress in the treatment of psoriasis in the last decade has been remarkable and a careful understanding of the strengths and limitations of these models can lead to better approaches for our patients.

APPENDIX

Psoriasis Therapy

Traditional systemic therapy. *In the context of psoriasis includes methotrexate, cyclosporine, acitretin, and prednisone.*

Biologic agents (biologics). Pharmaceuticals derived from living organisms such as animals and humans that target specific pathways in the immune system.

Acitretin. A synthetic retinoid available in oral form used for the treatment of psoriasis. Extreme caution must be used in women of childbearing potential due to its teratogenic effects (Pregnancy category X). Used in oral form.

Coal tar. Distilled tar mixtures of polycyclic aromatic and heterocyclic hydrocarbons and phenols derived from bituminous coal used as a topical treatment for psoriasis.

Corticosteroid. A hormone produced by the adrenal glands. Synthetic forms such as prednisolone, prednisone, and dexamethasone have similar biologic and chemical properties. Available for oral, injectable, and intravenous administration.

Cyclosporin (CsA). An immunosuppressant agent with inhibitory activity on T-lymphocytes commonly used postallogenic organ transplantation. Other uses in medicine include psoriasis, atopic dermatitis and many autoimmune diseases.

Goeckerman therapy. A classic psoriasis treatment regime consisting of crude coal tar and UVB light therapy administered in a clinic or hospital-based setting. Modified Goeckerman therapy combines the classic regime with other topical and systemic psoriasis treatments.

Methotrexate (MTX). An antimetabolite that inhibits the metabolism of folic acid. It has a wide spectrum of uses in medicine, particularly in cancer chemotherapy and immunosuppression in autoimmune diseases. Available for oral or injectable administration.

Phototherapy. The use of ultraviolet (UV) light for the treatment of various dermatoses. Narrowband UVB (NBUVB) includes wavelengths of UV light from 311 to 313 nm and is considered more effective and safer for the treatment of psoriasis and other UVB responsive dermatoses.

Psoriasis Scoring Scales

National Psoriasis Foundation Score (NPF-PS). A measurement that accounts for induration (of two representative target sites), body surface area compared to baseline, physician and patient global assessment scale, and patient itch score on a scale of 0 to 5. Total score range: 0 to 30.

Psoriasis Area and Severity Index (PASI). A measurement of erythema, thickness and scale for psoriatic lesions (score: 0 to 4) on four body regions (head, upper and lower extremities and trunk) which provides an approximate estimate of body surface area involvement. Scores range: 0 to 72. For clinical studies and medical therapeutics the goal is at least a PASI 75 (i.e., 75% improvement with therapy). Total score range: 0 to 100.

Physician Global Assessment (PGA). A measurement of overall erythema, thickness and scaling and body surface involvement compared to baseline on a seven-point scale (severe, moderate to severe, moderate, mild to moderate, mild, almost clear, clear). Total score range: 0 to 7.

Dermatology Life Quality Index (DLQI). The most common quality of life measurement used for psoriasis that accounts for symptoms, activities, occupation/vocation, social relationships, etc.) on a scale of 0 to 3. Total score range: 0 to 30.

Quality of Life (QoL). A comprehensive assessment of all physical, psychosocial, occupational well being.

Quality-Adjusted Life Years (QALY). A measurement of disease burden that accounts for quality of life (morbidity) and survival years (mortality) for a medical intervention.

Cost Comparison Analysis

Cost-benefit analysis. A comparison of cost of intervention (or medication) to the cost of the effects of intervention expressed in the same monetary values. Final measurement is a net benefit or cost-benefit ratio. It does not account for quality of life measures.

Cost-effectiveness analysis. An expression of the final effect of intervention (not in monetary values) similar to cost-utility. A commonly used health-related measure is the Incremental cost-effectiveness ratio (ICER) between two different interventions determined by the additional cost per life year gained. Health policy makers may use ICER thresholds to determine if an intervention is considered cost-effective and to be funded. ICER thresholds are variable between countries; the United

States and United Kingdom has ICER set at <\$50,000 per QALY and <\$30,000 per QALY respectively.

Cost-utility analysis. An expression of the final effect of intervention in generic values similar to cost-effectiveness analysis most often used by health policy makers. Examples include fixed units of health-related gain in quality-adjusted life-years (QALYs), additional life years, etc.

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Cost-effectiveness of Rosacea Treatments

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INTRODUCTION

One in three Americans has a dermatologic skin condition serious enough to require medical attention.¹ Nevertheless, there are major gaps in knowledge about the frequency, impact, etiology, and prevention of these diseases.¹ Rosacea is among the most common skin conditions dermatologists treat.² It affects more than 16 million Americans and presents itself as a challenging condition with multiple therapeutic options.³ Therefore, in this chapter we would like to narrow the knowledge gap by a presentation of rosacea's background and available evidenced-based treatment options.

METHODS

A systematic literature review was performed using PubMed of journal articles including a combination of the following key terms: rosacea, treatment, therapy, cost, and quality of life. Articles included in the review were published within the 1989–2010 period, the majority being published in 2009.

BACKGROUND

Clinically Defining Rosacea

Rosacea is a chronic inflammatory disease that affects the convexities of the facial skin.^{4,5} It typically presents with persistent erythema, flushing, edema, papules, pustules and telangiectasias of the face including the nose, cheeks, forehead, and chin.^{5,6} Affected extra facial areas are rare, but have been observed in locations prone to flushing and sun damage such as the ears, neck, upper chest, back, and the scalp.^{4,5,7,8} Secondary features include burning, stinging, edema, plaques, and phymatous changes.² In the long term, the disease can cause scarring and disfigurement, drastically affecting patients' quality of life.

Thus far, there is no laboratory benchmark test for rosacea, hence the difficulty of interpreting clinical and diagnosis data.² Despite the lack of precision, rosacea symptoms are classified by the expert panel into four 'sub-types': facial redness, bumps and pimples, skin thickening, and eye irritation.^{2,3} These translate into erythematotelangiectatic (ETR), papulopustular (PPR), phymatous, and ocular

rosacea.² Clinically heterogeneous, these phenotypes have one characteristic in common: the presence of chronic facial skin inflammation.⁹ Rosacea typically manifests itself in phases. First, transient erythema appears; then telangiectases, papules, and papulopustules develop; after which diffuse hyperplasia of the connective tissues and sebaceous glands are very likely to occur.⁸ Two other variants of rosacea not included in the classification are rosacea fulminans and granulomatous rosacea.⁷

Patients with rosacea most often present with flushing, itching, and sensitive skin.⁴ Some symptoms are more or less common in different racial groups. For example, papules and pustules are less common in African Americans. African Americans, however, are more prone to develop the granulomatous variant of rosacea.⁴ Despite the fact that there are over 16 million Americans with rosacea, the disorder is still not well understood.³ Strikingly, 78% of individuals have limited knowledge in recognizing and treating rosacea.³ Additionally, there are several dermatologic skin conditions that are similar to rosacea and need to be cautiously considered at diagnosis. Some of the conditions are acne vulgaris, seborrheic dermatitis, perioral dermatitis, contact dermatitis, photodermatitis, and lupus.⁷

Epidemiology

Rosacea affects 10% of the general population.^{4,10} It manifests itself in lighter skin populations.^{7,11} Hence, it is a very common disease in the United States and in the European Union (EU) countries.⁷ It is estimated that in the United States rosacea affects 1 in 20 adults, with certain ethnic groups being more prone to developing the disease than others.^{7,12,13} Some studies suggest that 4% of all rosacea affected patients are African-Americans, Latinos, or Asians.⁷

A lack of a uniform definition for the disease has limited exact reporting of its incidence. The peak incidence of the disease occurs during the fourth and fifth decade of life.^{12,14} Morbidity linked to rosacea usually occurs during the latter decade of life.⁷ The prevalence of the disease varies with different studies. It ranges from 0.5 to 10%.^{7,15} In a survey in Sweden the prevalence was found to be closer to the higher end, with females dominating the gender.^{7,16} Previous literature finds rosacea to be three times more

common in women, but more severe forms manifesting in men.^{8, 15, 16} Conversely, most recent data indicates both sexes to be similarly affected.¹⁵

Etiology

Rosacea is associated with a number of etiologic causes and inciting factors.⁴ The main mechanisms at cause are believed to involve an inflammatory process of the vasculature and pilosebaceous units.⁴ It can be triggered by a variety of factors such as food and beverages, weather and temperature, emotions, intense exercise, menopausal flushing, alcohol, medical conditions, and various skin care products.^{3, 9, 17} Furthermore, trigger factors are specific to each patient.¹⁷

Understanding the mechanisms of rosacea has been based both on scientific investigations and anecdotal evidence.² Some possible explanations include vascular changes, environmental factors, matrix degeneration, ultra violet radiation, reactive oxygen species, proteases, and microbial organisms such as *Demodex folliculorum* and *Helicobacter pylori*.^{2, 9} The latest molecular studies link innate immune response to the pathogenesis of rosacea.⁹ Triggering the innate immune system leads to an increase in antimicrobial molecules and cytokines in the skin.⁹ Cathelicidin is the unique molecule with some of its forms having the capacity to exhibit both vasoactive and proinflammatory properties, hence possibly affecting rosacea's descriptive events. Analysis of cathelicidin peptides in rosacea-affected individuals showed abnormal high levels of the peptides.⁹ Moreover, different forms of cathelicidin are found to be present in rosacea-affected individuals compared to those not affected. Laboratory results of skin inflammation when injecting mice with enzymes that produce cathelicidin or with peptides directly further support the linkage between cathelicidin and rosacea.⁹

There are questions yet to be answered. Approximately 40% of patients with rosacea have a relative with the disorder.¹⁷ Identification of genetic factors and gene loci that predispose affected individuals to rosacea are currently under investigation. Additionally, there is a need to understand the histologic and pathologic basis of papules and pustules and whether micro-organisms play a role in their development.¹⁷ Blushing is a neural-mediated function, therefore investigating rosacea's neurologic influences can aid toward the understanding of its pathogenesis.¹⁴ In harmony with this idea are studies suggesting an increased incidence of rosacea in Parkinson's patients.¹⁴

Quality of Life

Rosacea is a disfiguring condition that affects patients' quality of life (QoL).⁷ It can produce embarrassment, frustration, anger, stress, and depression in affected individuals.⁷ Balkrishnan et al. conducted a study investigating factors associated with the health-related quality of life (HRQoL)

in women with visible facial skin lesions, including rosacea. Findings indicate that facial blemishes are associated with significant impairment in the overall HRQoL, the effect of the lesions being mediated by self-perception and self-presentation characteristics.¹⁷ Additionally, strong correlations among fear of negative perceptions and poor HRQoL were identified.¹⁸ In a more recent study, Salamon et al. similarly shows that patients with rosacea have a lower HRQoL when compared to patients without rosacea.¹⁹

Because the facial skin is the predominant site affected, many patients express that rosacea negatively affects their social and professional interactions.² The 2007 National Rosacea Society Survey results indicate that 76% percent of the 603 respondents report their condition to lower their self-confidence and self-esteem, 41% to avoid public contact, and 70% with a more severe form of the disease report a drastic effect on their professional interactions.³ Disease-specific QoL instruments are useful in measuring patient-reported therapeutic impact of various types of treatments over time.¹⁰ Nicholson et al. developed and validated a reliable rosacea-specific instrument to more accurately measure the impact of rosacea on patient's QoL.¹⁰

TREATMENTS

Topical, Systemic, Laser/Light Therapies

Since the underlying cause of rosacea is not known, cure remains elusive.^{3, 7, 15} Therefore, treatment is targeted to control the symptoms.¹⁵ A number of therapies are available for the treatment of rosacea, including a single or combination use of topicals, oral medications, and laser/light therapy.^{4, 17} Examples of topical medications include metronidazole, sodium sulfacetamide and sulfur, azelaic acid, benzoyl peroxide, erythromycin, clindamycin, tacrolimus, and tretinoin.¹⁷ Out of these, the first three have been approved by the Food and Drug Administration (FDA) for the treatment of rosacea and the rest are used off label.¹⁷ Among oral medications, tetracyclines, macrolides, metronidazole and isotretinoin are the most commonly used.¹⁶ Minocycline and doxycycline are thus far the only two of the oral tetracyclines approved by the FDA for the treatment of rosacea.⁷ Laser and light therapies are also used, however, the high costs and limited insurance coverage prevent many patients from using laser/light treatment modalities.⁷

Although, there is no precise algorithm for rosacea treatment, tetracycline-type antibiotics are considered the gold standard. Together with topical metronidazole and azelaic acid, they are the most commonly used treatments.¹⁵ Azithromycin and minocycline-CR have been presented as possible treatments but not yet approved by the FDA.⁷ Doxycycline, the most traditional tetracycline used for the treatment of rosacea has proven to be safe and effective for short and long-term therapy while two topicals,

metronidazole and azelaic acid, have proven to be safe and effective for short-term therapy only.¹⁵ Light treatments with intense pulsed light and long-pulsed dye lasers have shown to be effective at decreasing erythema and eliminating telangiectasias.⁷ For the remaining therapy options, not enough effectiveness and safety data is yet available to make conclusive statements.¹⁵ Hence, improvements in the quality of studies evaluating rosacea treatments are desired.⁷ Furthermore, evidence for rosacea treatments in patients with darker skin is even scarcer. This is due to the fact that treatment of darker skin requires consideration of potential pigmentary alterations or keloids.⁷

The collection of rosacea treatments can be overwhelming to patients and physicians.⁷ Appropriate therapeutic strategies need to address clinical features, rosacea subtype, and the staging of the severity of lesions.⁷ Patients that have pre-rosacea symptoms can be treated with over the counter agents, while prescription therapy is most appropriate for primary and secondary rosacea features.⁷ Once sufficient efficacy is observed, oral therapy is discontinued and replaced with topical therapy.²⁰ When considering therapies for rosacea, FDA-approved therapies should be prescribed first, followed by all others.⁷

Because the four variants of rosacea (erythematotelangiectatic, papulopustular, phymatous, and granular) respond differently to various therapies, therapeutic implications are different among the phenotypes.^{2,17} Therefore, rosacea can be effectively controlled with therapy tailored to the specific subtype.²¹ For mild cases, topical metronidazole, sulfacetamide/sulfur, and azelaic acid are used, while combination therapy with oral tetracycline and topical agents is the first-line of choice for moderate papulopustular rosacea.²¹ For ocular rosacea, patients are often on long-term antibiotics and metronidazole gel.²¹ Inflammatory papules or pustules and erythematous components are treated with topical therapy, the most effective ones being azelaic acid and metronidazole.⁷ Rosacea that is refractory to topical treatments is targeted with oral antibiotics, the most commonly used being doxycycline 50 mg.⁷ Additionally, oral therapy should be considered for patients who exhibit inflammatory papules and pustules but without significant erythema.⁷ The most efficacious combination therapy is doxycycline and metronidazole gel 1%. This combination can be used by individuals with inflammatory and erythematous mild-to-moderate rosacea.⁷

Being constantly visible can produce a great deal of stress, frustration, and depression for the rosacea patient.⁷ Therefore, both symptomatic and psychological treatments are equally important.⁷ Educating patients about triggers and the controllability of the disease can help alleviate patient's psychological distress.⁷ Moreover, emphasis on continuous therapy is detrimental, as the damage is often progressive.⁷ Despite the overwhelming range of treatments available for rosacea, patients, physicians, and pharmacists can all take an active role in managing the disease and improving the QoL.

Cost-Effectiveness Studies

There is a dearth of rosacea cost-effectiveness studies. This could be attributed to several factors. One is the diverse treatment spectrum and paucity of head-to-head trials directly comparing the different treatment options.²² Second, is the lack of a standard success measure in clinical trials. Success could vary from one clinical study to another because of the differences in patient population, drug dosages or schedules, and concurrent treatment.²² Thirdly, even medications in the same category have different tolerability and adverse effects profiles, which in turn could affect patient adherence to a treatment regimen and influence efficacy and cost.²²

Thomas et al. evaluated the cost-effectiveness of the most common therapeutic regimens for rosacea. More specifically, the study investigated the cost necessary to achieve successful treatment of rosacea in 15 weeks based on efficacy data from clinical trials. Results indicate metronidazole 1% once daily gel among topicals and tetracycline 250 mg/day among oral agents to be the least costly.²² Sodium sulfacetamide/sulfur 10% and 5% lotion twice daily was the second least costly, while oral isotretinoin was on the opposite end of the spectrum. Moreover, topicals were found to have similar annual direct costs among each other, while the costs among oral agents were found to be much more dispersed.²²

Sun avoidance behavior is an important part of treatment for any rosacea patient and can be cost effective.¹⁷ Behavioral sun avoidance and the use of sunscreens present a low cost option that can be integrated into the treatment of rosacea patients. A broad-spectrum sunscreen is recommended to be applied daily alone or in combination with a topical agent, most commonly 1% metronidazole. In fact, several rosacea topical agents already contain sunscreen ingredients. Rosacea patients need to practice caution as some sunscreens can cause irritation and produce erythema. This can be minimized by mixing sunscreen preparations with protective ingredients such as silicones.¹⁷

The long-term implications of rosacea, such as rhinophyma and scarring of the face require surgical or laser intervention. These therapies present a substantial cost and patients should be advised that ineffective treatment of rosacea might require treatment by these modalities. Laser and light-based therapies can also be effective for treatment of the vascular erythema component of rosacea, but, are expensive.¹⁷ Laser therapy or treatment with intense pulsed light (IPL) can range from \$200 to \$600 USD per treatment depending on the surface area treated. These treatments and generally require 1 to 5 IPL sessions are generally needed to be repeated after a few weeks.¹⁷

Rosacea treatments are presented in Tables 70-1, 70-2 and 70-3. Table 70-1 lists various treatments available with evidence for efficacy and safety. Many published trials have limitations in the quality of evidence-based efficacy. This is due to poor design and clinical applicability.²⁰ The

TABLE 70-1—Evidence-based Treatments for Rosacea^{7,20,23}

Treatments	Evidence-Based Efficacy & Effectiveness	Safety/Side-effects
TOPICALS		
Metronidazole 0.25%, 0.75%, 1% cream, gel lotion (e.g., MetroCream, MetroGel) [†]	<ul style="list-style-type: none"> Efficacy and safety confirmed via multiple blinded, split-face, and open-label vehicle controlled studies.²³ Based on 9 trials assessing the efficacy via physician's global evaluation and patient-assessed measures, metronidazole was found to be more effective than placebo.^{7,20} Study with questionable design showed superiority of metronidazole plus sunscreen versus placebo.²⁰ 	<ul style="list-style-type: none"> Cases of allergic contact dermatitis.⁷ Mid-pruritus, skin irritation and dry skin.²⁰ Based on the results of the 9 trials, there were no significant differences in the number of adverse events between metronidazole and placebo.²⁰
Pimecrolimus 1% cream q.d.-b.i.d. (Eidel)	<ul style="list-style-type: none"> Applied b.i.d., 50% patients had clear skin and most showed at least modest improvement in a 6 wk pilot study.⁷ Four-to-eight week study found it to be no more effective than the vehicle creams.⁷ 	<ul style="list-style-type: none"> Cutaneous adverse events such as local burning, stinging, and itching present in <20% of patients.⁷
Clindamycin 1% lotion, gel, solution, pledget (Cleocin) and Erythromycin 2% solution, ointment, pledget (Akne-Mycin)	<ul style="list-style-type: none"> Data supporting the use of the two for rosacea treatment is limited.²³ 	<ul style="list-style-type: none"> Concern for emergence of antibiotic resistance.²³
Azelaic acid 15% gel [†]	<ul style="list-style-type: none"> Between-patient and within-patient trials showed clear improvement for those using azelaic acid compared to placebo.⁷ Azelaic acid 15% is clinically superior to 0.75% metronidazole in improving inflammatory lesions and erythema.⁷ Efficacy and safety supported by multiple blinded and vehicle-controlled trials when applied b.i.d.²³ A different study found that when compared to topical metronidazole, there was no statistically significant difference between the two. Physicians did however rate the azelaic acid group with a higher improvement score.²⁰ Four trials comparing azelaic acid with placebo ranging from 9-12 wks demonstrated azelaic acid superiority via physician and patients' assessments in three of the trials.²⁰ Increased strengths up to 20% have been used effectively, but not yet approved by the FDA.⁷ 	<ul style="list-style-type: none"> Azelaic has greater potential for irritation compared to 0.75% metronidazole.⁷ Although the number of adverse events was lower in the metronidazole group, there was no difference in the severity of the adverse events among the two groups.²⁰ Based on the four trials, the azelaic acid group experienced more side effects, including burning, stinging, and irritation.²⁰
Sodium sulfacetamide 10% alone or with sulfur 5% combination, lotion, cream, pledges, short-contact preparation, cleanser (Sulfacet) with or without sun-blocking agent [†]	<ul style="list-style-type: none"> Randomized vehicle-controlled and comparative studies confirm its efficacy and safety based on reductions in inflammatory lesions and erythema.²³ Sodium sulfacetamide 10% and sulfur 5% combination versus placebo was found to have superior improvement potential.²⁰ 	<ul style="list-style-type: none"> Dryness, erythema, and pruritus are some of the most common ones.²⁰
Permethrin cream 5% q.d.-q.w. (Nix)	<ul style="list-style-type: none"> Shown to be effective in case-reports of refractory rosacea diagnosed as demodicosis.²³ When compared to metronidazole, permethrin was inferior in terms of efficacy and safety as it showed no effect on pustules.²⁰ 	
Crotamiton 10% q.d.-t.i.d. (Eurax)	<ul style="list-style-type: none"> Suggested to be useful in treating rosacea when linked to <i>Demodex folliculorum</i>, but unlikely to be successful at eradicating the organism.⁷ 	
1-Methylnicotinamide 0.25% b.i.d. (MNA+)	<ul style="list-style-type: none"> Applied for 4 wks, improvement was rated as moderate to good in 26 of 36 cases and 7 patients showed no clinical response.⁷ 	

Treatments	Evidence-Based Efficacy & Effectiveness	Safety/Side-effects
Benzoyl peroxide 5%/erythromycin 3% gel	<ul style="list-style-type: none"> Compared two 4 wk therapies with metronidazole gel and found similar efficacy results.²⁰ 	
Benzoyl peroxide 5%/clindamycin 1% gel	<ul style="list-style-type: none"> Compared to placebo, patient's global assessment indicate much to slightly better improvement in outcomes for 12 wks while the physician's global assessment indicate a definite improvement.²⁰ The combination of benzoyl peroxide 5%-clindamycin 1% (BenzaClin) has been shown to be effective.²³ 	<ul style="list-style-type: none"> Burning and itching, well-known side-effects of benzoyl peroxide, were reported.²⁰
SYSTEMICS		
Doxycycline, USP (Oracea Capsules) 40 mg once daily (30-mg immediate-release and 10-mg delayed-release beads) [†]	<ul style="list-style-type: none"> Phase 3 pivotal trials demonstrate efficacy and safety for treatment of inflammatory rosacea in adults.²³ Is effective in treating inflammatory papules and pustules, but not erythema that is associated with rosacea.⁷ 	
Tetracycline 500 mg b.i.d. (Sumycin); Doxycycline 50-100 mg b.i.d. (Vibramycin); Minocycline 50-100 mg q.d. or b.i.d. (Minocin); Minocycline time-release 45, 90, 135 mg (Solodyn) [†]	<ul style="list-style-type: none"> All the therapies are utilized based on extensive clinical experience and peer-reviewed literature including some clinical trials.²³ These are the most currently used antibiotics by dermatologists.⁷ Minocycline time-release is indicated to treat only inflammatory lesions of non-nodular, moderate-to-severe acne vulgaris in patients 12 yrs and older and it is the first weight-based antibiotic oral therapy for rosacea.⁷ Oral oxytetracycline and tetracycline were compared with placebo in a total of 3 trials ranging from 4-6 wks reporting superior effectiveness for tetracyclines via physician assessment and insufficient evidence of superiority according to patients' assessment.²⁰ Additionally, 3-6 mo remission achieved upon interruption of the treatment was attributed to repeated courses of same dose therapy.²⁰ Two 8 wks studies showed no statistical significant difference in treatment between oxytetracycline and metronidazole cream.²⁰ 	<ul style="list-style-type: none"> Long-term therapy with minocycline beyond 6 mo carries an increased risk of pigmentary deposition.⁷ Possible side effects associated with tetracycline: gastrointestinal, photosensitivity, candidal vaginitis, reduction in oral contraceptive efficacy.²⁰
Isotretinoin 0.15-2 mg/kg q.d. (Accutane)	<ul style="list-style-type: none"> Reports of effectiveness for severe and/or refractory cases of rosacea.²³ Although effects may be delayed, when compared to standard therapy, a reduction in the number of papules is evident within 2 weeks.⁷ Most significant results noted in younger patients with less severe manifestations of the disease.⁷ Useful in treating and reducing phymatous changes.⁷ 	<ul style="list-style-type: none"> Blood testing of serum lipids recommended as part of clinical lab monitoring.²³ Pregnancy avoidance as precaution in female patients needed.²³ Dry sensitive skin, dry eyes, pruritis, dermatitis, myalgia, elevated liver enzymes, cholesterol and triglyceride elevation.²⁰ Possible fetal abnormalities when women become pregnant.²⁰ Routine monitor of cholesterol, liver functions, and triglycerides necessary.²⁰
Azithromycin 250 mg t.i.w. (Zithromax)	<ul style="list-style-type: none"> It is thought to act as an antioxidant and appears to be useful for treating rosacea.⁷ 	<ul style="list-style-type: none"> Minimal side-effects and lack of drug interactions could make it a good alternative for rosacea patients.⁷
Omeprazole (Prilosec) and a combination of two of the following: clarithromycin (Biaxin), metronidazole, or amoxicillin (Amoxil)	<ul style="list-style-type: none"> This is the systemic treatment for <i>Helicobacter pylori</i> advocated as a possible therapy for rosacea.⁷ Oral metronidazole alone was compared to oral oxytetracycline in one study and there was no difference at 12 wks among the two groups evaluated by physician and patient assessments.²⁰ 	<ul style="list-style-type: none"> In the metronidazole vs. oxytetracycline comparison there were no adverse events reported.²⁰

(Continued)

TABLE 70-1—Evidence-based Treatments for Rosacea^{7,20,23} (Continued)

Treatments	Evidence-Based Efficacy & Effectiveness	Safety/Side-effects
Penicillin 2.4 mL units/day, erythromycin 250-500 mg two-four times/day, amoxicillin or ampicillin 100-500 mg daily or twice/day (Principen), metronidazole 250 mg two-three times/day, dapsoe 50-200 mg once/day	<ul style="list-style-type: none"> Proved efficacy in treating rosacea but not commonly used clinically.⁷ 	<ul style="list-style-type: none"> Gastrointestinal, photosensitivity candidal vaginitis, reduction in oral contraceptive efficacy.²⁰ Metronidazole could be linked to mutagenicity and neuropathy.²⁰
Acitretin (Soriatane), ketoconazole (Nizoral), spironolactone (Aldactone), prednisone	<ul style="list-style-type: none"> Reported to be effective.⁷ 	
Rilmenidine	<ul style="list-style-type: none"> No significant difference in treatment when compared to placebo.²⁰ 	
Oral contraceptives, some psychoactive drugs, clonidine, naloxone, aspirin, beta-blockers, ondansetron, and cyclooxygenase-2 (COX-2) inhibitors, and selective serotonin reuptake inhibitors (SSRIs)	<ul style="list-style-type: none"> Reported for treatment of flushing in rosacea patients.⁷ 	
Oral contraceptive chlormadinone acetate/mestranol (Ovosiston) and the antiandrogen agent cyproterone	<ul style="list-style-type: none"> Suggested as effective hormonal treatments for rosacea.⁷ 	
COMBINATION THERAPIES		
Doxycycline with topical metronidazole gel 1%	<ul style="list-style-type: none"> Effective and well tolerated in reducing inflammatory lesion counts in mild-to-moderate rosacea affected patients.⁷ 	
PHOTOTHERAPY		
Multiplexed laser	<ul style="list-style-type: none"> Appears to help in reducing erythema and telangiectasia.⁷ 	
Intense pulse light (IPL) 550-670 nm	<ul style="list-style-type: none"> Particular useful for ERT.⁷ 	
Flash lamp-pumped, long-pulse dye laser, and the potassium-titanyl-phosphate laser	<ul style="list-style-type: none"> May be used to treat facial telangiectasias.⁷ 	
OTHER		
Benzoyl peroxide acetone	<ul style="list-style-type: none"> Compared to placebo, showed improvement on all measures.²⁰ 	<ul style="list-style-type: none"> Irritation and burning reported in both groups.²⁰
NONMEDICAL THERAPIES		
Moisturizers	<ul style="list-style-type: none"> Clinical assessments confirmed by biophysical measurements such as electrical capacitance, transepidermal water loss, and lactic acid stinging test suggest them as contributors to the restoration of skin barrier.⁷ Skin dryness, roughness, and desquamation were much improved. Skin sensitivity was significantly reduced.⁷ Skin properties enhanced.⁷ Skin discomfort relieved.⁷ 	
Kinetin (N6-furfuryladenine) 0.1% lotion b.i.d.—a plant cytokinin	<ul style="list-style-type: none"> Helps restore skin barrier function.⁷ Beneficial for improving rosacea symptoms, especially for patients with mild-to-moderate inflammatory rosacea.⁷ 	

Treatments	Evidence-Based Efficacy & Effectiveness	Safety/Side-effects
Combination of Oral minocycline, spironolactone, and Chibixiao (a Chinese herb)	<ul style="list-style-type: none"> Combination was found to be superior to minocycline and spironolactone alone in a trial.⁷ 	

[†] FDA approved for rosacea treatment; q.d., once daily; b.i.d, twice daily; q.i.d, four times daily; q.w., weekly (every week); t.i.w., three times weekly; mg, milligram; kg, kilogram; nm, nanometers; mln, millions; wk(s), week(s); mo, months.

TABLE 70-2—Rosacea Treatments by Subtype¹⁷

Rosacea Subtype	Therapy
Erythematotelangiectatic	<ul style="list-style-type: none"> Patients have barrier disruption and sensitivity to topical products. If minimal barrier dysfunction, metronidazole or sodium sulfacetamide-sulfur, or a combination of the two should be applied in the morning followed by sunscreen. Evening application of barrier emollient and tretinoin may be used concomitantly. For persistent irritant reactions, scaling and bright erythema: physical sunscreen and barrier-protective emollient twice daily in addition to oral antibiotics may be beneficial. Barrier protection along with isotretinoin 10 to 20 mg/daily for 3 to 4 months may lessen flushing episodes and erythema. For severe irritant responses, application of high-potency steroid ointment twice daily for 1 week, followed by once daily for 1 week and tacrolimus ointment in combination with oral minocycline once daily could be used. This regimen is replaced by topical medical regimen after 1 to 2 months. Surgical and light therapies can be selected as first-time therapy if affordable to patients.
Papulopustular	<ul style="list-style-type: none"> Initial therapy involves a combination of oral and topical antimicrobial agents. Skin sensitivity is less common, therefore, all topical therapeutic options are well tolerated. Oral tetracycline is used while isotretinoin is rarely needed. Long-term management is comprised of topical agents only. Example of an effective combination of topical regimen is metronidazole, sodium sulfacetamide-sulfur, azelaic acid, or benzoyl peroxide followed by sunscreen every morning and by a protective emollient and tretinoin cream in the evening. Vascular lasers and intense pulse light are adjunctive therapy options.
Glandular	<ul style="list-style-type: none"> Topical antimicrobials such as benzoyl peroxide and benzoyl peroxide combinations work quickly and are well tolerated. Oral therapy comprising mostly of oral tetracyclines targets papules and pustules and is continued for 1 to 3 months. Mild to moderate glandular rosacea is managed with topical retinoids and topical/oral antimicrobial therapy. Severe inflammatory or nodulocystic disease can be controlled with isotretinoin followed by topical tretinoin long-term management. Increased sebum production, large pore size, and thickened skin is most often controlled with spironolactone 25 to 50 mg daily, oral contraceptives, and isotretinoin.
Phymatous	<ul style="list-style-type: none"> Early to moderate phymatous rosacea is treated with isotretinoin. Advanced forms of the disease are targeted by surgical therapies, such as heated scalpel, electrocautery, dermabrasion, laser ablation, tangential excision combined with scissor sculpturing, radiofrequency electrosurgery, often in combination with isotretinoin.

most commonly used therapies such as doxycycline, minocycline, isotretinoin, or laser therapy, although used in practice, lack quality RCTs data.²⁰ Furthermore, an interesting observation in rosacea studies is that clinicians report higher satisfaction scores with different treatment

modalities more often than patients do. Patients' lower satisfaction scores could be affecting their adherence levels to therapy.²⁰ Table 70-2 lists the most common therapy sequence for each rosacea subtype and Table 70-3 lists rosacea treatments by subtype.

TABLE 70-3—Rosacea Treatments by Symptom²⁰

Symptoms	Treatments	
Limited pustules/papules	Topical therapies	Metronidazole, clindamycin lotion, permethrin 5% cream, tretinoin cream, sulfacetamide 10%/sulfur 5%, azelaic acid 15% gel and 20% cream.
Limited pustules/papules	Proposed therapies	Tacrolimus, topical NADH (reduced form of β-nicotinamide adenine dinucleotide).
More severe skin lesions	Oral antibiotics	Tetracycline, ampicillin, metronidazole, erythromycin.
Vascular symptoms	Pulse dye laser, intense pulsed light	
Severe or persistent rosacea	Oral isotretinoin	13-cis-retinoic acid
Flushing control	Oral hypotensives	Clonidine, rilmenidine
Rhinophyma	Oral medications, laser therapy, surgical intervention	Low-dose isotretinoin
Ocular rosacea	Oral antibiotics, topical	Tetracycline, metronidazole, fusidic acid gel

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Cost Effectiveness of Treatment for Non-Melanoma Skin Cancer

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INTRODUCTION

According to recent statistics from the National Cancer Institute, approximately 1 million new cases of nonmelanoma skin cancer (“NMSC”) were diagnosed in 2009¹. This figure is in line with a study completed in 1994 that estimated between 900,000 and 1.2 million cases of nonmelanoma skin cancer in that year alone². Given the steady occurrence rate of these cancers over the past decade, many have declared nonmelanoma skin cancer an epidemic with an increasing incidence in people under the age of 40^{3,4}. While several treatment modalities exist, an increased attention to cost has forced many physicians to balance therapeutic efficacy with expense.

Skin cancers can be treated by various methods including cryotherapy, electrodesiccation and curettage, topical chemotherapy, surgical excision, Mohs micrographic surgery (“MMS”), radiation therapy, and photodynamic therapy. The common goal of each of these treatment modalities is to provide a high cure rate and satisfactory cosmetic and functional result with minimal risk in a cost-effective manner. This chapter reviews the dermatologic literature relating to cost and utility. It is important to note that the majority of studies published to date have been cost comparisons, which differ from cost effectiveness analyses in that they do not take into consideration the differing outcomes of the treatment modalities⁵. This is a limitation of the current data and should be noted by the reader.

It is assumed that for all treatment modalities, the tumor must first be correctly diagnosed. Therefore, an initial evaluation (CPT code 99203), a skin biopsy (CPT code 11100), and permanent section for dermatopathology evaluation (CPT code 88305) must be added on to any cost discussed. In order to estimate these costs, the 2010 Medicare reimbursement rate can be used as a benchmark. Therefore, at baseline, before a nonmelanoma skin cancer is treated, the average cost across the United States is \$95.49 for an initial evaluation in a nonfacility setting, \$92.56 for a skin biopsy and \$93.81 for dermatopathology evaluation, based on an average of 91 reimbursement rates available at the Centers for Medicare and Medicaid Services website. The total cost

is thus \$281.86 to the health care system before the tumor itself is treated.

In this chapter, cost of cryotherapy, electrodesiccation and curettage (“EDC”), radiation therapy, surgical excision and Mohs micrographic surgery (“MMS”) will be considered keeping in mind that not all of these modalities can be used for all histologic tumor subtypes.

CRYOTHERAPY

Cryotherapy is a common procedure used to treat premalignant lesions but can also be used to treat superficial basal cell carcinomas and squamous cell carcinoma in situ. It relies on destruction through necrosis, which results from a rapid freeze followed by a slow thaw process for malignant lesions⁶. Success rate for cryotherapy treatment of malignant lesions varies and is dependent on size of the tumor and thickness. If the optimal tumor is selected, the 5-year recurrence rate may be as low as 1%⁷ or as high as 7.5%⁸. Variations in these rates have also been published and may be higher with individual dermatologists. If recurrence is to occur, it is likely to happen within the first two years and thus patients treated with this modality should be followed carefully for at least 3 years after treatment. Side effects include alopecia, atrophy, hypopigmentation, milia, hyperpigmentation, change of sensation, blistering, and incomplete treatment.

After initial evaluation and biopsy, one must assume an office visit for treatment, destruction of the malignant lesion and at least one follow-up visit to ensure complete treatment. Therefore, in addition to an initial cost of \$281.85 for diagnosis, an additional expense of two office visits (CPT code 99212) and the destruction of a malignant lesion (CPT code 11726 for example) must be considered. According to the Centers of Medicare and Medicaid website, the average reimbursement for a level two office visit across the nation in a non-facility is approximately \$39.06 and a destruction of a malignant lesion on the trunk, arms or legs (as an example) is approximately \$88.56. The total cost for cryotherapy of a single nonmelanoma skin cancer is thus the cost of diagnosis, \$281.85 plus two office

visits, and one treatment of \$166.68, making the total cost on average \$448.53.

This cost does not take into consideration any morbidity from cryotherapy, incomplete treatment, or recurrence. It should also be noted that cryotherapy cannot be used for the majority of nonmelanoma skin cancers, so that while it is a relatively low cost treatment modality, its utility is limited.

ELECTRODESICCATION AND CURETTAGE

Electrodesiccation and curettage is frequently used to treat NMSC less than 1 cm on the body and occasionally on the face. In this technique, three passes of EDC are performed using a monopolar electrosurgical device and a curette. Tissue destruction is created 3 to 4 mm beyond the clinical margin. Although this technique can be quickly performed in the office, recurrence rates up to 20% occur, requiring Mohs micrographic surgery for treatment⁹.

Rogers and Coldiron estimated costs for treatment of NMSC by varying techniques and concluded that EDC is the least expensive¹⁰; cryotherapy was not included in the analysis. The authors compared multiple therapeutic modalities for a BCC on the cheek of varying sizes (0.6 cm, 1.1 cm, 2.1 cm and 3.1 cm) as well as for a SCC on the forearm of similar varying sizes. They estimated costs by comparing the relative value unit ("RVU") for each procedure and then multiplied this total by the national average conversion factor of \$38 per RVU. The authors concluded that for a BCC on the cheek, the cost of treatment via EDC was on average \$471 (range: \$389-\$573). For a SCC on the forearm, the range was \$323 - \$472, with an average of \$392. The additional cost of initial office visit, biopsy, and diagnosis were not included in these numbers, nor was follow-up or cost of treatment after recurrence.

While EDC is cost effective, its utility, like cryotherapy is limited. Tumors that are treated should be well circumscribed, less than 1 cm in size and primary. Aggressive subtypes of BCC such as the morpheaform variant are not recommended for treatment with this technique. Side effects include scarring, prolonged healing time, incomplete treatment, and hypopigmentation. This technique is rarely used on the face, further limiting its widespread potential for treating all NMSC.

TOPICAL IMIQUIMOD

In 2004, the FDA approved Aldara cream (Graceway Pharmaceuticals, Bristol, TN) for the treatment of superficial basal cells located on the trunk, neck, and extremities measuring less than 2.0 cm in diameter in immunocompetent adults. The medication has shown clinical and histologic clearance for superficial basal cells, however 5-year follow-up data is inadequate to predict recurrence rates.

Karve et al. performed a literature review and published that for superficial basal cell carcinomas, imiquimod is

more cost effective than surgical intervention¹¹. The authors acknowledge a lack of long-term follow-up as a limitation to interpretation of their results.

Similarly, the HEIS study group-evaluated imiquimod versus surgical excision treatment for a superficial BCC measuring less than 2 cm¹². The decision analysis model assumed imiquimod 5% cream application five times a week for 6 weeks and an efficacy rate of 82%. The authors estimated that approximately 36 sachets of imiquimod would be used to complete treatment and assumed an initial dermatology visit with biopsy followed by an average of 2.5 visits after starting treatment and one visit to the primary care physician. The efficacy of surgical excision used for comparison was based upon review of 209 medical records collected from both dermatology and nondermatology services and was 97% and 90% respectively. The study showed that the mean cost per patient cured by surgical excision was 676 Euros when using a dermatologist and 1051 euros when a nondermatology service was used. For topical imiquimod, the cost per patient was 621 euros when treatment was directed by a dermatologist and 676 euros when treatment was directed by a non-dermatologist. Thus the savings of imiquimod use compared to surgical excision in a dermatologic setting was approximately 55 euros and 375 euros when the two modalities were compared in a nondermatologic setting. Under the Spanish national healthcare system, imiquimod was favorable in cost compared to surgical excision specifically for superficial basal cell.

Rogers and Coldiron estimated the cost for treatment of a BCC on the cheek with imiquimod, assuming a 20% recurrence rate and 5% initial incomplete clinical response based on phase III and 2-year follow-up studies^{13,14}. These authors assumed 30 sachets of medication were needed at a cost of \$648. For a 0.6 cm BCC on the cheek, cost was approximated at \$929. For a BCC on the cheek up to 2.1 cm in size (beyond the size recommended by the FDA to treat), cost was \$950. For a SCC on the arm, imiquimod treatment cost was \$896 for a 0.6 cm lesion and \$939 for a 2.1 cm lesion. The average cost for the BCC group (size ranging from 0.6 cm to 3.1 cm) was \$959 and for the SCC group (similar size range) was \$931. This average was more expensive than treating the SCC on the arm with excision (average \$907), but less expensive than excision on the face for a BCC (average \$1006). The authors note that these cases were for illustrative purposes only as neither advocated imiquimod use for tumors other than superficial BCC in immunocompetent patients.

Treatment failures, long-term follow-up, quality-of-life measures, patient morbidity and time away from work, while under treatment have not been taken into consideration in any imiquimod studies to date evaluating cost. Nonetheless, initial expense analysis indicates that it is reasonable to use imiquimod cream for ill-defined superficial basal cells on the body and carefully selected areas on the face. It is not advisable to use it as a first line for nodular

BCC on the face or for squamous cell carcinomas. As with all treatments, patient selection, and tumor consideration are paramount for consideration.

RADIATION THERAPY

While radiation therapy is used in select circumstances to treat nonmelanoma skin cancers, it is by far the most expensive treatment modality, as it is relegated to the hospital or facility setting and requires careful monitoring, follow-up and multiple treatment sessions. A standardized regimen for treating NMSC does not exist and most studies have varying fractional doses and treatment sessions. However, radiation can be chosen as a modality depending on the patient's other comorbidities, tumor location, and subtype of tumor. Rogers and Coldiron estimated radiation therapy using a total dose of 61 Gray subdivided into 3.5 Gray doses would be approximately \$3460 for treating a BCC on the cheek and \$3431 for a SCC on the arm. Given the complications with radiation therapy and its failure rate of 7% and recurrence rate of 10%¹⁵, it is safe to assume that this treatment modality is to be reserved for specific cases (e.g., perineural invasion) where other treatment modalities cannot be considered.

SURGICAL EXCISION

Surgical excision is the standard against which all other treatment modalities for NMSC are compared in terms of cost. The standard margin used for primary BCC and SCC anywhere on the body is at least 4 mm. After removal, the specimen is sent for permanent sectioning and the wound is immediately repaired either with a primary closure or a flap or graft. Cost for this procedure can increase if the specimen is sent for frozen sectioning or if the excision takes place in an ambulatory surgery center or hospital operating room. Recurrence rates after excision of NMSC have been published, but vary from 5% to 18%¹⁶⁻¹⁸. A published systematic literature review estimated a 5.3% 5-year recurrence rate after surgical excision for primary BCC¹⁶. For SCC, this rate ranges from 5% for low-risk lesions to 10.9% and 18.7% for high-risk lesions on the lip and ear, respectively¹⁷. Positive margins are either treated with re-excision or via Mohs surgery. Recurrence is typically treated with Mohs. In addition, if the procedure takes place in the hospital setting, preoperative clearance and anesthesia costs are an addition. Several studies have evaluated the cost of surgical excision versus other therapeutic options. As noted above, for superficial basal cells, Dominguez et al. demonstrated that under the Spanish healthcare system, surgical excision by a dermatologist is more costly than topical imiquimod 5% cream used five times a week for 6 weeks¹².

Rogers and Coldiron estimate an average cost of \$1006 for surgical excision with permanent sections and immediate repair for a BCC on the cheek compared to \$907 for

the same treatment for a SCC on the arm. The authors assumed a rate of positive margins after initial excision to be 11% and the long-term recurrence rate to be 10% based on previous studies^{19,20}. Once a patient is treated in an ambulatory surgery center and the specimen is evaluated by frozen section, the average cost increases to \$2334 for the BCC scenario and \$2200 for the SCC case. In the hospital setting, excision with frozen section costs an average of \$3085 for a BCC on the cheek (range: \$2543-\$3893 depending on size of the case) and \$2680 for a SCC on the forearm (range: \$2166-3413 depending on size). This represents a 195% -207% increase in cost over excision in the office. Rogers and Coldiron also estimate preoperative laboratory work prior to operating room excision to be about \$191 and medications and supplies for the operating room to be approximately \$200. All of these costs are of course in addition to the initial evaluation, biopsy, and diagnosis done in the dermatologist's office. Therefore, if traditional surgical excision is considered, value is best achieved when the procedure is performed in the office with permanent sections and immediate repair.

In 2004, Bialey et al.²¹ performed a cost comparison analysis of MMS versus traditional surgical excision. The study was performed at a tertiary care referral center in Connecticut. In their report, the authors looked at costs alone without taking into consideration effectiveness – in other words patient quality of life, time away from work and co-morbidities were not calculated. The group limited itself to evaluating tumors that met published criteria for MMS removal – tumors on the face and ear. They took into consideration the multiple surgery reduction policy and included preoperative laboratory tests and x-rays when calculating facility fees. However, the authors measured lesion size, rather than excision size for coding, a method which changed in 2003 (data was collected from 1999 – 2001). They evaluated 40 tumors located on or near the nose, 16 on the cheek, 14 on or in front of the ear, 12 on the forehead, 7 on the canthus and around the eye, 7 on the temple and 2 on the lip. The setting for traditional surgical excision was the office (57%), ambulatory surgery center (39%) and operating room (4%). There was also a distribution of repair types taken into consideration for Mohs (primary closure 49%, local flap 4%, granulation 44%, and skin graft 2%) and for traditional excision (primary closure 56%, local flap 29%, granulation 12%, skin graft 2%, and forehead flap 1%). The results showed the mean Mohs cost per patient for removal of facial and auricular NMSC to be \$937 and surgical excision to be \$831 (P=.04). After accounting for the cost of a second procedure for positive margins after permanent sections and excision, the cost increased to \$1029 if Mohs was used for the second procedure along with a Mohs repair, and \$944 if the positive margin was treated with another excision and an ear-nose-throat specialist repaired the wound. Thus, when comparing the cost of a second excision plus repair by a specialist to Mohs in the first place, the costs are quite comparable

(\$944 vs. \$937). There was no value assigned to patient well-being during this time or satisfaction, which is valued during a cost-effectiveness analysis and not a cost analysis. For this reason, members of this study group lead by Anne Seidler published subsequent data in 2006.

Seidler et al. compared Mohs surgery to surgical excision for facial and auricular NMSC and found that in these cases, where there is a potential for high-risk tumors because of the location over embryonic fusion plates (the “H” of the face), excision was less cost effective than Mohs²². In this study, the authors included a measurement of quality-adjusted life years based on focus group interviews and estimated costs based on a prospective sample of 98 consecutive patients with NMSC on the face and ears. The authors assumed a 5% recurrence rate of primary BCC after excision and 1% after Mohs. Each patient acted as their own control. An otolaryngologist evaluated all 98 patients and anticipated the size of the margins and repair type he would use if the patient were to undergo a standard excision (just as had been done in the 2004 study). This evaluation was then compared with the actual documented Mohs margin. If the Mohs margin extended beyond the otolaryngologist’s estimate, the authors assumed the theoretical excision margins would have been inadequate. The costs assumed that 57% of the excisions took place in an office setting, 39% in an ambulatory surgery center and 4% in an operating room. The group also assumed a distribution of repair types after Mohs and excision that consisted of healing by second intent, primary closure, flap and graft. Overall, the study concluded that surgical excision was nearly \$300 more expensive than Mohs for these specific areas and Mohs had a greater effectiveness over surgical excision by approximately 3 weeks of optimal quality of life. One limitation of this study was that the authors modeled cost based on a granulation rate of 45%, which is higher than the distribution of Mohs repair types reported by others, which show that Mohs surgeons tend to use primary closure in 69% of cases, granulation in 11%, flaps in 14% and grafts in 6%^{23,24}. Nonetheless, in comparing the two therapeutic modalities side by side, excision for tumors of the face is less cost effective than Mohs surgery. This data is critical because it not only looks at cost, but cost plus efficacy measured as patient satisfaction, morbidity, and quality of life.

Bentkover et al. compared the cost of Mohs with that of surgical excision using rapid cross-sectional frozen section for treatment of BCC on the head and neck²⁵. The authors found a cost savings for excision over Mohs, however, their evaluation was based on a capitated practice setting. A Mohs surgeon was not part of their group and all Mohs surgical procedures were outsourced as fee-for-service, thereby incurring an increased cost. The authors reported a \$150 to \$454 cost-savings benefit to excision over Mohs per tumor. For excision, all facility and excision fees were covered under global capitation, which left only the pathology fees to compare to the outsourced cost of Mohs. For

this reason, the findings of this study are discordant with others as detailed below.

MOHS MICROGRAPHIC SURGERY

Mohs micrographic surgery has been recognized to provide the highest cure rates for both primary and recurrent nonmelanoma skin cancers. Its technique relies on interpretation of frozen tissue sections by a trained MMS surgeon and translation of these findings to the clinical setting. The technique is tissue sparing and guidelines have been developed for its optimal use that include criteria such as tumor type, size, location, and recurrence²⁶. There are no guidelines, however on who may bill or perform Mohs and the result has been what many feel is an over-utilization of the MMS method. When analyzing billing codes paid by Medicare this is evident, as Mohs codes represent a disproportionate number of claims. During the past 15 years, MMS has become so prevalent that it now ranks as the single largest expenditure for all physician procedures²⁷. The utilization rate of the former main Mohs surgery CPT code, 17304 increased from 80,000 procedures in 1993 to 450,000 in 2005²⁸. While the number is alarming, it should be noted that the number of skin biopsies in the same period of time also doubled. The statistics have thus prompted a number of researchers to analyze the cost of MMS compared to traditional surgical excision for nonmelanoma skin cancer.

In 1998, Cook and Zitelli published a report analyzing a group of 400 consecutive patients referred to their office for treatment of skin cancer²⁹. The majority of patients were for basal cell carcinoma treatment (n=306), followed by squamous cell carcinoma (n=64). This study included, however, 21 patients referred for malignant melanoma. The authors compared MMS versus traditional excision in terms of cost. For each patient, they included the cost of initial evaluation, skin biopsy, permanent section pathology for diagnosis and 5 years of follow-up not included in the global postoperative period. They also assumed that tumors treated in the office by excision and permanent section would have a positive surgical margin in 11% of cases and require re-excision, additional permanent section pathology, and repair. This assumption was based on an earlier study by Cataldo et al.³⁰ Furthermore, the authors compared MMS to excision in the office with frozen section control and excision in an ambulatory surgical facility with frozen section control. In the latter two cases, 21% of tumors were assumed to have at least one positive margin as prior studies had shown that the average skin cancer excision using frozen section control required 1.21 stages to obtain negative surgical margins³¹. The authors also factored in permanent sections to confirm negative margins in all frozen section excision cases. Lastly, the authors accounted for recurrence rates, which they assumed to be 10.1%¹⁸ for traditional surgical excision and 1.0% with MMS¹⁸. For these recurrent cases, they

added on the average cost of MMS in the cases presented in the series.

Cook and Zitelli concluded that MMS is cost effective on all body locations compared to other methods of surgical excision. The difference between office excision with permanent section and MMS was less than \$100, using 1996 RBRVS values for Western Pennsylvania. On the head/neck region the cost for office excision was calculated to be \$1201 versus \$1278 for MMS and \$905 on the trunk versus \$964 for MMS in the same location. Office excision with frozen section was more costly with ambulatory surgical facility excision and frozen section being the most expensive. The authors attribute the value of Mohs to the bundling of excision with microscopic evaluation that occurs in the MMS codes. In addition, there is an inestimable cost associated with tissue preservation, especially on the face. Bumstead and Ceilley reported that conventional surgery removes 180% more tissue than MMS in primary cutaneous malignancies and 347% more tissue than MMS in recurrent tumors³². Smaller wounds can often heal by secondary intention thus eliminating the cost of repair and if repaired, the smaller wounds often lead to better cosmetic and functional results. The authors conclude that MMS is thus a cost-effective treatment with a high intrinsic value that compares favorably to traditional surgical excision.

Rogers and Coldiron agreed with such findings. In their study, MMS averaged \$1263 to treat a BCC on the face and \$1131 to treat a SCC on the arm. These authors discuss that the loss of the multiple surgery reduction exemption has decreased the cost of MMS by 9-25%. Although MMS is still slightly more expensive than office-based excision, they felt that Mohs had certain unquantifiable positive effects. For example, MMS has the lowest recurrence rate of all treatment modalities, resulting in a decreased number of second excisions for positive margins and fewer office visits. In addition, MMS results in a small surgical defect with a consequently smaller repair³³. The authors thus concluded that the slight increase in cost compared to surgical excision was of value, thereby giving MMS greater cost effectiveness.

Mosterd et al. evaluated 5-year follow-up data and evaluated the economics of MMS for recurrent basal cell carcinoma of the face³⁴. The study followed 198 patients with primary BCC treated with MMS and 199 patients with primary BCC treated with surgical excision. They also compared the cost of treatment of 102 patients with recurrent BCC treated with surgical excision to 100 patients with recurrent BCC treated with MMS. At 60 months, there were 11 recurrences in the primary BCC arm (4 after MMS and 7 after excision). In the experimental arm treating recurrent BCCs, 31 of 102 tumors were not completely excised after primary excision. After re-excision, 8 remained incompletely excised and had to be treated with MMS. At 60 months, there were 12 recurrences in the recurrent BCC study population; two after MMS and 10 after surgical excision. Given the 5-year data, the authors then calculated the

incremental cost effectiveness ratio ("ICER") for treating a primary BCC versus a recurrent BCC with MMS. This ratio is used in health economics to assess the value of a new therapy compared to a traditional therapy based on efficacy and cost. The group concluded that the ICER for primary BCC was 23,454 euros, while for recurrent BCC it was 3,171 euros per recurrence avoided. Since no threshold exists for the treatment costs of BCC, the group used a comparison value of hospital costs associated with treating a recurrent tumor (2568 euros). Thus, although MMS for primary BCC may not be cost effective, for recurrent BCC, the data suggests that it should be considered a cost-effective treatment.

Mosterd's study is important for several reasons. First, it highlights the need to assess cost effectiveness using a timeline of at least 5 years. For example, Essers et al. examined the cost-effectiveness of MMS versus surgical excision for facial basal cells but followed primary BCC cases for 30 months and recurrent cases for 18 months rather than 60³⁵. The authors found that the recurrence rate between MMS and surgical excision for primary BCC at 30 months was 0.0091. They divided the mean difference in cost by this effect difference and found an incremental cost of 29,231 euros per recurrence avoided. For recurrent BCC, the effect difference was 0.032, leading to an ICER of 8,094 euros. This is double the value when compared to 60-month data. The differences highlight the need for long-term studies to truly evaluate efficacy for any treatment modality. Second, these two studies give insight to an important assumption when discussing cost analysis – ultimately the payor and system in which the treatment is delivered make the difference. For example, in the two studies reviewed above, both Mosterd's group and Essers group evaluated data in the Netherlands where the Mohs margin was 3 mm rather than the standard 1 mm used in the United States³⁶. Furthermore, both studies utilized a separate pathologist to evaluate tissue, thereby increasing costs. Lastly, the data in both papers is derived from patients who were treated in a hospital setting, which studies in the United States have shown to be the most expensive treatment method for tumor extirpation.

CONCLUSION

Multiple options exist for the physician when considering treatment of a NMSC. Because of the high incidence of these tumors, cost must be evaluated when choosing a therapeutic modality. While cryotherapy is the least expensive of all options, its utility is severely limited. Similarly, EDC and imiquimod provide acceptable results in comparison to cost, but again, can only be used in specific situations. Radiation is the most expensive, but if it is called for, there are not appropriate other substitutes for that kind of therapy. The real decision for the practitioner is whether to recommend excision or MMS for patients with NMSC. It is clear from the published data that if one is to recommend MMS based on recommended guidelines, it is cost

What We Know

- The high incidence of nonmelanoma skin cancer is considered an epidemic with an increasing rate in people younger than the age of 40.
- Practitioners in the current US healthcare system must consider cost when recommending therapy for cutaneous malignancies.
- Cryotherapy is the least expensive option for NMSC destruction but is limited in utility.
- Electrodesiccation and curettage is inexpensive, however, the morbidity associated with this treatment makes it unsuitable for destruction of tumors on the face and those greater than 2 centimeters.
- Imiquimod cream is a relatively new entrant into the marketplace for nonmelanoma skin cancer treatment and although it is comparable in cost to surgical excision, long-term recurrence rates are not yet available limiting analysis of its cost effectiveness.
- Surgical excision performed in the office with immediate repair is the most cost-effective for tumors that are not in high-risk areas. If margins return positive or there is recurrence, this modality loses its cost effectiveness completely.
- Mohs micrographic surgery is comparable in cost to traditional surgical excision with frozen section, as well as surgical excision performed in an ambulatory surgery center or the operating room. Compared to the latter two cases, it can be argued that Mohs is of better value and more cost effective. For tumors on the face, Mohs as the primary treatment modality is more cost-effective in terms of pure dollars and in terms of quality-adjusted life years for the patient.

effective. Even off the face, MMS is comparable in cost to traditional surgical excision. The key for the dermatologist is to consider cost in the overall picture of the patient's health, tumor type and location. Cost should be balanced with efficacy as the dermatologist decides the surgical, destructive or treatment modality most appropriate for the tumor site on their patients.

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Evidence Based Approach



Adherence to Treatment

72

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INTRODUCTION

Physicians today have the luxury of a veritable armamentarium of medications that have been tested in clinical trials and found to be highly efficacious for their respective indications. Yet, in clinical practice, many of these same medications fail to affect the same degree of success in treatment.¹ This is true particularly in the management of many chronic diseases and has left many an experienced physician scratching their head in dismay. In a long-term study of psoriasis patients on psoralen-UVA (PUVA) therapy, Jones-Caballero et al. incidentally observed that of patients who had been switched from PUVA to biologic therapy, 42% still had moderate to severe disease at the close of the study. This was surprising given that the response rate of moderate to severe psoriasis in clinical trials is as high as 70 to 80%.² A similar disparity can be found with use of topical calcipotriene for psoriasis, which used alone in clinical trials results in clearing or almost clearing of plaques in 70% of patients.³ In contrast, in clinical practice calcipotriene must be used in combination with topical corticosteroids to achieve comparable results.⁴ In fact, the explanation for such consistent discrepancies between responses in clinical trials versus clinical practice is simple, it is adherence. Adherence is defined as the extent to which patients follow the agreed-upon recommendations of their health care provider, is at the root of both the variability of response to treatment between individual patients and the discrepancy between response in clinical trials versus clinical practice.⁵ This chapter will first examine a variety of dermatologic phenomena that can be explained by adherence, then outline measures of adherence, and finally discuss factors affecting adherence and strategies to improve adherence in practice.

TACHYPHYLAXIS

A classic tenet of dermatologic teaching has been that prolonged use of topical corticosteroids results in decreased response over time, a phenomenon known as tachyphylaxis. This has been attributed to a down-regulation of steroid receptors with repeated exposure, although it has been difficult to demonstrate in controlled clinical trials.⁶ In practice, tachyphylaxis can be successfully overcome by

switching to a different topical corticosteroid of comparable potency. This effective strategy for managing tachyphylaxis should raise a red flag about its etiology—if indeed the cause was down-regulation of steroid receptors, a simple switch to a different corticosteroid should not correct the problem, and yet it does. The best evidence suggests that tachyphylaxis is not “the more you use it, the less it works.” Rather, based on studies showing that patients’ use of topical medications decline over time,^{7–9} tachyphylaxis is likely a function of poor adherence: “the less you use it, the less it works.”¹⁰

ATOPIC DERMATITIS

It is not uncommon to find that children with severe atopic dermatitis (AD) refractory to all topical medications will clear rapidly during a short hospitalization in which they are treated only with topical triamcinolone. This is remarkable considering these children have often failed other more potent steroids and combination therapies, and yet it is a widely recognized phenomenon. Previous explanations proposed was a result of removing the child from exposure to dust mites or a stressful environment at home. The notion that spending the night in an unfamiliar hospital room is less stressful to a young child than their own home is preposterous. The actual explanation lies in adherence behavior. In fact, the evidence suggests these children get better in the hospital because they are actually getting the treatment. Krejci-Manwaring et al. studied adherence behavior to twice-daily 0.1% topical triamcinolone ointment in an 8-week study of children with mild to moderate AD. The medication was dispensed with a Medication Event Monitoring System (MEMS™) cap, which enabled the recording of every time and date the medicine was opened. Patients and their parents were not aware they were in a formal study and they did not know their adherence was being monitored until the end of the study. Over the 8-week study period, the overall adherence rate was 32%. This study minimized the effects of a clinical trial on patient adherence and thus was more representative of actual practice.⁹ It is no wonder then that patients eventually fail topical outpatient therapy and improve on mid-potency steroids during brief hospitalizations. Medications work much better when patients actually use them.

ACNE

Acne can be challenging to treat, in no small part, because many of the patients are teenagers and young adults. Achieving adherence in these patients can be even more challenging than doing so in adults. In a study on adherence behavior in college students to a variety of treatments, only 36% of students were found to complete their prescribed treatment; adherence to acne medication was even worse: only 12.5%.¹¹ Adherence rates were better in a 12-week clinical trial on techniques to improve adherence in teenagers to daily 0.1% adapalene gel. This study included four arms. The standard of care group had return visits at 6 and 12 weeks, the frequent visit group had return visits at 1, 2, 4, 6, 8, and 12 weeks, the electronic reminder group received a daily text message, or e-mail reminder to use their medicine, and the parental reminder group enlisted the parent to give the teenager a daily verbal reminder to use their medication. In the standard of care group, adherence started at approximately 70%, dropping to 40% over the course of the study. Adherence in the frequent visit group was slightly better, starting at 80% and dropping to 50% over the study period. Electronic reminders had minimal effect on adherence; rates were approximately equal to the standard of care group. Interestingly, parental reminder had a negative effect on adherence; adherence rates were lowest in this group.¹² Even in clinical trials, with a once daily medication and frequent visits, teenagers are only about 50% adherent with treatment. Adherence in clinical practice can be expected to be even less than that found in clinical trials. Predicting adherence rates of less than 50% (probably significantly less when treatment involves more than one medication), it is not surprising that treating acne in teenagers may result in suboptimal outcomes.

PSORIASIS

In surveys of psoriasis patients, reported adherence rates range from approximately 50 to 60%.^{13–16} Studies comparing self-reported adherence rates and rates obtained objectively via electronic medication monitors (like MEMS™ technology) consistently find that self-report significantly overestimates adherence.^{8,15,17,18} Carroll et al. found adherence rates of 55% versus 90%, as measured by MEMS™ and self-report, respectively⁸ Zaghloul et al. had similar findings: 61% versus 92%.¹⁵ Thus, the poor adherence rates of 57%¹³ and 61%¹⁴ from two anonymous surveys of psoriasis patients can be presumed to reflect even more abysmal actual adherence rates.

Even when given the added motivations found in clinical trials, including being paid for participation, having more frequent visits, and being told adherence is being studied, psoriasis patients still exhibit suboptimal adherence behavior. In an 8-week study of adherence in psoriasis patients, patients were instructed to apply 6% salicylic

acid gel (a combination gel with 0.1% tacrolimus ointment or placebo) twice daily. These patients were explicitly instructed that how they took their medicine would be monitored and they had four visits over 8 weeks. Initial adherence at 1 week was 85%, but dropped to 51% over the course of the study, for an overall rate of 55%.⁸ An ingenious Danish study used data from pharmacies to assess adherence in clinical practice. They found that psoriasis patients had the lowest adherence rates of all groups studied and that 4 weeks after being given a prescription, 44% of psoriasis patients had not even filled their prescription.¹⁹ Of the 56% who did fill their prescriptions, one can only imagine what smaller percentage then went on to actually use it as directed.

It has been suggested that the presence of particularly thick, rock-like, “coral reef” plaques in psoriasis is a marker for resistance to topical treatment, a sign of highly refractory disease, because the medication cannot penetrate. Coral reef psoriasis may be a marker of resistance to topicals, but it isn’t because topical treatments don’t penetrate: diseased skin has poor barrier function, even when hyperkeratotic.^{20,21} More likely, the patients who present with coral reef plaques are very nonadherent patients. When medication actually makes contact with these plaques, they respond quite well to treatment as was demonstrated in a case report.²² One might presume that patients with such severe disease would be highly motivated to get well and therein, would be more likely to use their medications. And yet, studies show that the opposite is true: patients with more severe disease exhibit lower adherence rates than patients with milder disease.^{14,15}

SCALP PSORIASIS

Scalp psoriasis can be one of the most frustrating conditions to treat, for both patients and providers. No matter what treatment or combination of treatments is tried, these patients do not seem to get better. Looking at the problem through the lens of adherence helps in understanding why scalp psoriasis is so difficult to treat. Adherence research shows that people will not take antibiotics for even a week for a bothersome problem and that patients do not do well using their topical medications for chronic skin diseases. Applying medications to the scalp is far more difficult than any of these other tasks. Treating scalp psoriasis is difficult, not because the disease itself is recalcitrant to treatment, rather, it is difficult because it is nearly impossible to get patients to apply medications to their scalp.

Many other explanations have been offered to explain refractory scalp psoriasis. It is widely thought that the fact that patients scratch and Koebnerize their scalp can explain scalp psoriasis, yet this same action on other areas of their bodies does not cause the psoriasis plaques to be as uniquely resistant to treatment as is scalp psoriasis. Others propose that the scale of scalp psoriasis blocks

the penetration of topical agents.¹² In fact, normal scalp exhibits percutaneous absorption similar to the axilla;²⁰ penetration is likely even greater in diseased scalp. Clinical trials support this; rapid clearance of scalp psoriasis is achieved when topical clobetasol is applied to the scalp without the use of keratolytic medications.^{23,24} Scalp psoriasis responds very poorly to treatment for three simple reasons: poor adherence, poor adherence, and poor adherence.

SKIN CAP

"Flash, March 10, 1997" Writing in their diary published in *Cutis*, Drs. Walter and Dorinda Shelley wrote, "The big news is Skin Cap, coming out of Spain, now sweeping the country as an over-the-counter spray therapy for psoriasis. Make no mistake about it, it is good. One of our friends said, "I don't have any psoriasis practice. They all use Skin Cap.... No longer do the patients need steroids inducted, ingested, or injected, and any more methotrexate or PUVA visits. It seems unbelievable that a product not even requiring prescription can be so effective."²⁵ Skin CapTM was advertised as a zinc pyrithione spray also containing the detergent sodium lauryl sulfate. The product showed unprecedented efficacy. It was only later discovered that the product actually contained clobetasol propionate. This surprised dermatologists because the same ingredient in ointment form was commonly used to treat psoriasis, with far less impressive effect. Moreover, the widely accepted teaching was that an ointment vehicle was more effective than a drying spray. It was speculated that the zinc was acting synergistically with the clobetasol, accounting for the increased potency of Skin CapTM. A study was done in which lesions on both sides of the body were treated with clobetasol foam. One side also received zinc pyrithione spray and the other side the spray vehicle. They found that the zinc spray was of no added benefit.²⁶

The dramatic results achieved by Skin CapTM are well explained by adherence. The spray worked better than clobetasol ointments did in practice because patients used it more and the reasons for this improved adherence illustrates some important principles in adherence. The spray was easier to apply and better tolerated than a messy ointment. Patients probably felt more comfortable because they had less fear about side effects (no one told patients it contained a strong steroid). Compared to an over the counter medicine, clobetasol sounds very scary when prescribed with the warning "This is the most powerful steroid in existence and using it too much is dangerous." Finally, patients may have been more likely to use Skin CapTM because they paid for it themselves. People in general are more likely to use or value something when they buy into it. Thus, what seemed to be a revolution in psoriasis therapy in effect was actually a revelation in understanding how much adherence mediates the relationship between treatment and outcome (Figure 72-1).

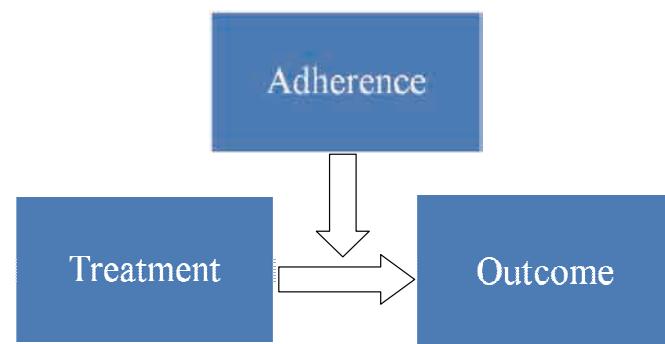


FIGURE 72-1 Adherence mediates the relationship between treatment and outcome.

MEASURES OF ADHERENCE

Because adherence has such a powerful affect on outcome, it is critical that providers monitor adherence. Adherence may be measured in a variety of ways including self-report, pill counts or medication weights, serum drug levels, using pharmacy data, and using electronic monitors. As previously mentioned, in clinical trials on adherence, rates obtained by self-report grossly overestimate rates obtained more objectively using electronic monitors.^{8,15,17,18} Unfortunately, while ideal for trials, electronic monitors are not practical for assessing adherence in clinical practice. Pharmacy data may be useful for objectively determining if patients procure medication, but they are a step removed from whether the patient uses the treatment, in addition to not being particularly practical for providers.

In clinical practice, blood test monitoring for drug levels is a straightforward and objective approach, however, this often overestimates adherence because patients tend to be better about using their medications around the time of an office visit, a phenomenon called "white coat compliance" (one of the most illustrative examples of this phenomenon is the tendency for people to floss more before going to the dentist).^{8,9,27} Counting pills or weighing a topical medication is a practical and seemingly objective way to assess adherence in practice, but patients are wily and may dump their medication to hide their poor adherence behavior. To improve the reliability of pill counts, instead of prescribing 60 tablets for a bid dosing and having the patient return in a month, either prescribe 70 tablets or prescribe 60 but have patients come back before the month is over. That way, if the bottle is empty, the physician can distinguish a bottle that has been emptied because of good adherence from one that was emptied to hide poor adherence.¹²

Although it is probably the least reliable, simply asking patients about their adherence to treatment may represent the most reasonable assessment option for most providers. An evidenced-based review of the literature was done to evaluate self-report instruments used to measure medication adherence in patients with chronic disease.¹⁷ Eleven self-report instruments for the measurement of adherence were identified. While all produced an estimate

of adherence that correlated with actual behavior, the correlation was not strong for any of the measures. None of the scales had been tested in patients who had dermatologic disease and/or used topical medications. Validity was higher for more objective adherence outcomes such as electronic monitoring systems as compared to self-report measures. To encourage honest self-reporting, the physician may ask, “It can be hard to use the medicine every day. How often are you missing doses: every day or every other day?” Moreover, as a rule, providers should probably just assume most of their patients are not using their medications as much as prescribed, nor as much as they report. Providers then can proactively minimize poor adherence in all their patients by adopting some basic strategies.

BARRIERS TO ADHERENCE

Many interacting variables influence adherence, which in turn mediates the relationship between treatment and outcome (Figure 72-1). The best evidence on causes of nonadherence in skin disease patients comes from work by Kimball and colleagues who studied the relative importance of factors contributing to nonadherence in psoriasis patients using topical corticosteroid. They surveyed 53 patients from the outpatient clinic. Reported nonadherence was 40% (although we suspect it was much higher as self-report underestimates how poor adherence is). The most important reasons for nonadherence included frustration with medication, efficacy, inconvenience, and fear of side effects. They also found that patients who reported not receiving instructions on topical treatment duration used their treatments longer than those who had received instructions.¹³

The factors that affect adherence can be classified as internal factors and external factors (Figure 72-2). The patient’s motivation to get better (or lack thereof) is a critical internal factor: some patients may not be motivated, a common factor underlying poor use of sunscreens in young people. The effects of skin cancer typically do not occur until later in life, something teenagers do not think about. As mentioned earlier, one might expect that patients with more severe disease would be more motivated to use their medications, while in actuality, data shows these patients are less likely to be adherent.^{14,15} Resignation may be a common cause of treatment failure in patients with chronic diseases like psoriasis, as evidenced by how many prescriptions go unfilled.¹⁹ Many people with psoriasis do not even come in for treatment, having given up hope, while others come in for the office visit, but don’t use the recommended treatment (or may not even purchase it) because they feel it is hopeless.

Conversely, patients may be motivated to get better but may not have the tools to effectively adhere to treatment. Often patients are not given adequate instructions on how to use their medications,²⁸ and even when they are, many

Internal Factors	External Factors
<ul style="list-style-type: none"> • Age • Poor motivation to get well • Secondary gain from illness • Feeling of hopelessness/ resignation about condition • Poor understanding of the disease • Unrealistic or inaccurate expectations of treatment • Psychiatric comorbidities • Lack of trust in the doctor • Lack of trust in or fear of the treatment • Fear of side effects 	<ul style="list-style-type: none"> • Weak physician-patient relationship • Complex treatment regimen (frequent dosing and/or multiple agents) • Poorly tolerated vehicle • Side effects and toxicities • Slow-acting medication • Cannot afford treatment • Limited access to treatment • Inadequate instructions provided on how to use medications • Long interval between follow-up visits

FIGURE 72-2 Factors contributing to poor adherence.

patients forget the instructions they were given. It generally takes about 6 minutes after leaving a doctors’ office for people to forget the instructions. Psychiatric comorbidities like depression may interfere with patients’ ability to carry out their treatment. Age is another important factor as children and teenagers are less likely to be adherent with treatment. Patients’ understanding of their disease and their expectations for treatment can play a critical role, as does their understanding of the treatment itself and expectations about side effects. Patients may not use treatments because they do not trust their doctor, the medical profession, or medications. Of profound importance is the patient’s trust in their doctor and the quality of the doctor-patient relationship. Seventy percent of adherent patients reported that they were using their medication because they believed their doctor was a compassionate advocate.²⁹

Many external factors influence adherence as well, including regimen complexity, treatment cost and availability, topical vehicle, and medication side effects. The time it takes a medication to work is critical, as is the patient’s response to treatment. For example, if a medication takes weeks to work, but the patient is expecting a “quick fix”, then that patient may stop using the medication, thinking that it failed. Conversely, if the patient has rapid initial success with a particular treatment, he or she may be more likely to continue using it. Other important considerations over which physicians have considerable control include the quality of the physician-patient relationship, plans for follow-up visits, and clarity of instructions provided. In general, while it is easy to write a prescription, it is much harder for the patient to follow through. For every patient, with every treatment, we should anticipate potential barriers to adherence and take steps to minimize them before they interfere with treatment. In dermatology, with all the topical medications we prescribe, it is far more difficult to adhere to medication than it is in other fields where only a pill may be needed.³⁰

STRATEGIES TO IMPROVE ADHERENCE

A Strong Doctor-Patient Relationship is Essential to Good Adherence

A wide variety of interventions may be sensible for improving patients' adherence behavior, although few have been rigorously studied. The doctor-patient relationship provides the critical foundation on which good adherence is built. As mentioned earlier, a majority of adherent patients attribute their good adherence to having a caring provider.³¹ Impressions began as soon as patients walk in the door. The office should have a pleasant appearance, with friendly staff. Posted signs regarding payment and insurance should be avoided as they send the wrong message about priorities. In the patient encounter, body language is important. The physician should make eye contact and smile. Patients feel less rushed and perceive a visit as lasting longer when the physician sits down.²⁹ Utilizing active listening techniques conveys the message that the physician cares. Similarly, laying hands on a patient during an examination provides tangible evidence to the patient that they are receiving a careful examination; using a lighted magnifier is another prop that can be used to reinforce this perception. Providing contact information when patients have questions later reinforces the message that the patient is cared for. Incorporating these basic steps into practice helps to provide the foundation of a strong doctor-patient relationship, which in turn facilitates good adherence and good patient outcomes (Figure 72-3).

Initial Adherence Fosters Long-term Adherence

Another avenue to good adherence lies in the ability to achieve good initial adherence (Figure 72-4). To this end, a promising approach appears to be the use of an office visit.²⁷ White coat compliance is a well-characterized phenomenon in which patients use their medication better around the time of office visits.^{32,33} A study was done to improve adherence and outcomes in patients with AD. The study attempted to achieve better adherence in patients

with AD by combining use of an easy-to-apply medication (instead of a traditional ointment) and more frequent return visits. Forty-one subjects with mild-to-moderate AD were treated with desonide hydrogel 0.05% twice daily, and disease severity was measured at baseline and weeks 1, 2, and 4. In order to improve adherence in the first week, subjects were told to expect a follow-up phone call on day 3. Adherence was measured in the study using electronic monitors. In contrast to the behavior of atopic patients treated with triamcinolone, in whom adherence drops by about 60-70% in 3 days, mean adherence to the desonide hydrogel declined much more slowly, from 81% on day 1 to 50% by day 27. The investigators concluded that the easier to use vehicle, the increased follow-up, and the good efficacy achieved by better adherence in the first days/week of treatment contributed to the better adherence outcomes. A literature review by the authors identified 15 studies, which commented on the relationship between adherence and office visits; 14 of 15 studies found that office visits had a positive effect on adherence.

Much in the same way that first impressions are important, seeing good results early on will cause the patient to trust their doctor, to trust in their medication and to continue using the treatment long term, thus achieving better long-term adherence. A fast-acting medicine should be used when possible; if a slow acting medication is necessary, pair it with a fast acting medication initially to help secure good initial adherence. Ensure patients get the best results by giving them the tools to use their medications correctly. Instructions for use of medication can get complicated quickly in addition to the fact that patients forget 50% of verbal directions given during a visit.³⁴ Prevent confusion by providing clear written instructions with all medications.

Incorporating a new habit into everyday life can be challenging—even the most motivated individual may forget to use their medicine. Simple memory aids may help patients maintain good adherence. A common suggestion is to tie the medication to an already established habit. This could mean taping a topical acne medication to the toothpaste tube or placing topical antifungal medication on top of the shoes. The effect of daily reminders has been studied in several clinical trials. A study on teenagers with acne examined the effect of several interventions, including daily

- Office staff should be friendly and professional
- Office is clean and well-maintained
- Posted signs convey message that patient care is the priority
- Make eye contact, smile, and shake hands with the patient
- Sit down during the encounter
- Do not interrupt the patient's opening monologue
- Be an active listener
- Show empathy
- Touch the patient's skin during examination
- Solicit patient input and questions
- Give patients contact information

FIGURE 73-3 How to create a strong doctor-patient relationship.

- Use fast-acting medications; if a slow-acting medication is being used, pair it with a fast-acting medication initially
- Provide written instructions on treatment
- Educate the patient about their condition and provide realistic expectations for treatment outcome
- Schedule an early follow-up visit
- Use motivational interviewing techniques
- Help the patient to identify memory aids to help them remember to use the medicine

FIGURE 74-4 Ways to secure good initial adherence.

reminders, on adherence to daily 0.1% adapalene gel. Daily electronic reminders via e-mail or text message had no effect on adherence, with rates comparable to the standard of care group. The intervention of more frequent office visits resulted in the best adherence rates, while daily reminders from parents actually resulted in worse adherence rates than no intervention at all.¹² Contrary to the prior study, Armstrong et al. found that an electronic reminder, in the form of daily text messages, was a very effective intervention to improve adherence to daily sunscreen use. They asked 70 adult volunteers from the general population to apply sunscreen daily for 6 weeks; half of participants received a daily text message reminder. Measuring adherence using electronic monitors, they found a mean adherence of 30% in the control group versus 56% in the group that received text messages.³⁵ Perhaps the disparate results of the two studies can be attributed to the study population, suggesting that text message reminders are helpful for adults but not teenagers. Nonetheless, memory aid strategies can be helpful in improving adherence; which memory aid will work for a given patient will vary, so some experimentation may be necessary.

Treatment Regimen Can Make or Break Adherence

Treatment choice is abound with implications for adherence (Figure 72-5). Perhaps the most straightforward way to improve adherence is to simplify treatment. Many skin conditions, including acne, are treated with multiple treatments. Combination products are now available that simplify treatment and can improve patients' adherence. This was tested in acne patients by assessing adherence to a combination topical medication applied once daily compared to daily applications of two separate generic subcomponents. In this randomized trial, 26 teenagers with mild to moderate acne vulgaris received 12 weeks of once daily clindamycin phosphate 1.2%–tretinoin 0.025% gel (CTG) or separate daily applications of clindamycin and tretinoin (C gel + T cream). Adherence was monitored in the study objectively using electronic monitoring caps. The CTG group had a median adherence of 88% compared to only 61% in the C gel + T cream group. In addition to using combination treatments, once or twice daily dosing regimens may achieve better results than more frequent dosing. Consider the psoriasis patient with coral reef plaques: while our instinct in these patients may be to add penetration enhancers or switch to more potent and risky treatments, adding additional medicines is counterproductive if poor adherence was caused by the complexity and time-consuming nature of the initial treatment. Paring down the regimen, these patients often achieve rapid improvement using a treatment that had previously been “ineffective.”¹² Simplifying treatment regimens may be a valuable means of improving adherence behavior.

- Explain all treatment options clearly
- Involve the patient in choice of treatment
- Solicit the patient's opinion and beliefs about treatment options
- Choose a vehicle that the patient will use
- Create a simple treatment regimen: use less frequent dosing and combination products when possible
- Explain side effects and use them to advantage when possible
- Be aware of the cost of medicines and do not prescribe medications that the patient cannot afford
- Ensure the patient can access the treatment

FIGURE 72-5 Treatment considerations to optimize adherence.

In the case of topical medications, selection of the appropriate vehicle is essential. The traditional teaching that ointments are the most effective vehicles for dry skin conditions like psoriasis has been debunked. A literature review of outcomes in psoriasis patients treated with clobetasol in a variety of vehicles revealed that ointments had comparable, rather than superior efficacy.³⁶ Lessons from Skin Cap™ and scalp psoriasis illustrate the fundamental principle that the most effective vehicle is the one the patient is most willing to use.

Side effects of treatment are important to consider, including both real and perceived side effects. The strength of the physician-patient relationship may help overcome patients' fears. A simple discussion with a trusted physician can reassure the patient that the proposed medication is safe enough to use. Unexpected side effects can quickly lead to discontinuation of a medication. Forewarning patients that burning or dryness is a normal reaction to the medication and will subside with use—or better yet, that such a reaction is “a sign the drug is working”—may keep patients from discontinuing treatment. In fact, if the patient is experiencing such a side effect, it means he or she is using the medication, and thus it probably is working.²⁹

CONCLUSION

There is very strong evidence that nonadherence is a ubiquitous problem in dermatology. The cost of poor adherence and resulting treatment failure is high, resulting in prolonged morbidity, medication switches, and office visits. Estimates suggest that poor adherence costs in excess of 100 billion dollars annually in the United States and is responsible for 10% of all hospitalizations.^{37–39} Physicians should expect some degree of poor adherence in all patients and should proactively address adherence in treatment planning. There is not yet enough evidence to make an adherence treatment plan for every situation. Adherence behavior is very complex and affected by a multiplicity of factors. Improving adherence is, at this point, largely an art, rather than an evidence-directed matter. Some generalizations can be made. However, first, we ought to assume that our patients may not use their medication as directed unless we take great pains to see that they do. We should give our patients the sense that we are trustworthy, caring

doctors committed to helping them get well. We should involve them in the choice of treatment, finding a treatment regimen and delivery system they feel they can live with. We should not overemphasize risks, and we should help patients see improvement quickly, often by encouraging

good adherence with a follow-up visit or other contact shortly after initiating treatment. Making sure the patient uses the medicine well, initially improves patients' trust in the medication, and encourages more regular use, in turn, improving outcomes.

What We Know

- Patients' responses to treatment are quite variable. Poor adherence to treatment may account for much of the variability.
- Many patients are poorly adherent to topical treatment.
- Patients' self-reported adherence behavior often overestimates true adherence.
- Patients often don't fill their prescriptions.
- When patients do fill their prescriptions, they often do not take the medication as directed.

- Use of topical medications often declines over time, and this may be the best explanation for the commonly observed phenomenon of "tachyphylaxis" to topical corticosteroids.
- Physicians can improve their patients' adherence behavior.
- Text messages and office visits increase patients' adherence to treatment.

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Ethnic Issues in Evidence-Based Dermatology

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INTRODUCTION

There has been an increased interest, by dermatologists, in learning about conditions as they relate to skin of color. However, a study found that from 1996–2005, teaching events at annual meetings of the American Academy of Dermatology (AAD), focusing on skin of color, have remained at 2%.¹ According to the US Census Bureau, the United States will be more racially and ethnically diverse by midcentury, with the nation projected to be composed of 54% minority by 2050.² There have been efforts to elucidate structural/functional differences, reactions to the environment (ultraviolet radiation, chemicals, pathogens, trauma, medications, etc.), uncommon conditions that present commonly (in certain ethnic groups) and common conditions that present uncommonly in those of darker skin pigmentation. Additionally, efforts have been made to understand differences in access to healthcare, clinical research and health insurance, by the federal government, to impact healthcare disparities. It is our effort in this chapter to highlight the meaning of skin of color, followed by a discussion of ethnic issues as they relate to epidemiology and healthcare disparities in dermatology and then conclude with a brief overview of the structure and function and cutaneous reaction patterns of skin of color.

DEFINITION OF SKIN OF COLOR

According to the Skin of Color Society, skin of color is defined as those individuals of Asian, Hispanic/Latino, African, Native American and Pacific Island descent.³ Another definition states that skin of color identifies individuals of particular racial and ethnic groups who share similar cutaneous characteristics and disorders, as well as reaction patterns to those disorders and other cutaneous stimuli, with individuals generally having darker skin hues.⁴ The term “ethnic skin” has also been used interchangeably in the scientific literature to denote all groups other than Caucasian.

The above descriptions warrant a discussion of the meanings of the words “race” and “ethnicity.” Race, as defined by the Oxford dictionary, as each of the major divisions of humankind, having distinct physical characteristics

or a group of people sharing the same culture, language, etc; an ethnic group.⁵ The Oxford dictionary defines the term “ethnic” as a group of people having a common national or cultural tradition.⁵ The definitions of race and ethnicity vary; however, according to the source.

The use of race in science and medicine have been a topic of considerable debate. This stems from the origins of the term, with the term first used by human divisions created by Carolus Linnaeus and the proper term first used by Johann Blumenbach, in the 18th and 19th centuries. Linnaeus divided humans into four main groups: (1) Europeans (2) Americans (3) Asiatics and (4) Africans. His description of Europeans as “fair...gentle, acute, inventive...governed by laws” is in stark contrast to “obstinate, content free” Americans, “sooty, severe, haughty, covetous” Asians, and “crafty, indolent, negligent” Africans.⁶

Blumenbach first used the term “race” in his classification of humans into five divisions: (1) Caucasian (2) Mongolian (3) Ethiopian (4) American and (5) Malay. Blumenbach felt that “in the same way that we classify races and generations of horses and poultry, of pinks and tulips, so also, in addition, must we class the varietes of mankind which exist within their common original stock.” In his description of “Negroes,” he states:

I am of the opinion that after all these numerous instances I have brought together of negroes of capacity, it would not be difficult to mention entire well-known provinces of Europe, from out of which you would not easily expect to obtain off-hand such good authors, poets, philosophers, and correspondents of the Paris Academy; and on the other hand, there is no so-called savage nation known under the sun which has so much distinguished itself by such examples of perfectibility and original capacity for scientific culture, and thereby attached itself so closely to the most civilized nations of the earth, as the Negro.⁷

The classifications of the above individuals, whether positive or negative, started divisions that exist to the present day. This had led some scientists and physicians to support the abandonment of the usage of race, seeing it as a social and cultural construction devoid of scientific or anthropologic evidence, in preference of the usage of ethnicity or no descriptor at all.^{8–10} As a matter of fact, the

American Anthropological Association, in a 1999 position paper, stated that:

It has become clear that human populations are not unambiguous, clearly demarcated, biologically distinct groups. . . . Throughout history whenever different groups have come into contact, they have interbred. The continued sharing of genetic materials has maintained humankind as a single species. Any attempt to establish lines of division among biologic populations is both arbitrary and subjective.¹¹

Despite the debate, the Office of Management and Budget (OMB), of the Federal government continues to recognize a minimum of five racial categories: (1) American Indian or Alaska Native (2) Asian (3) black or African American (4) Native Hawaiian or Pacific Islander and (5) white. The OMB also recognizes two ethnic categories: (1) Hispanic or Latino or (2) Not Hispanic or Latino. In a statement, they mention that the racial and ethnic categories should not be interpreted as being primarily biologic or genetic in reference, but may be thought of as social and cultural characteristics, as well as ancestry. They further state that respondent self-identification should be facilitated as much as possible. They give no definition of race/ethnicity, or of the categories mentioned above.¹²

In the field of dermatology, individuals of particular “races” may range in skin pigmentation from light to dark, making generalizations of dermatologic disease into specific “races” problematic. However, until more appropriate descriptors of skin pigmentation become available, we will continue the rest of the chapter using the broad categories defined by the federal government, realizing that those descriptors have their limitations.

EPIDEMIOLOGY OF SKIN DISEASES IN DIFFERENT ETHNIC GROUPS

Efforts to quantify the number of patients presenting with certain skin conditions in different ethnic groups has proven difficult because of the lack of large comprehensive datasets. Most of the data is derived from retrospective analyses of private or academic clinic patient populations. This leads to difficulties with extrapolation because of the effects of patient demographics, referral patterns, clinic expertise, clinic location, etc. leading to variations.

If we take the epidemiologic descriptors incidence and mortality, we find that varying federal statistics (Surveillance Epidemiology and End Results [SEER]) are available for melanoma, nonepithelial skin cancer, mycosis fungoides (and Sézary syndrome), cutaneous T-cell lymphoma and Kaposi sarcoma. Prevalence data are incompletely available for melanoma and not available for the rest within that dataset. Data representing reasons to visit a dermatologist may be seen in the National Ambulatory Medical Care Survey (NAMCS) and the National Health and Nutrition Examination Survey (NHANES). We will begin with SEER data on cutaneous melanoma and then briefly explore the

NAMC and NHANES studies, and lastly mention observations from private clinics.

Cutaneous melanoma accounts for approximately 78% of the skin cancer deaths in the United States. SEER data from 2002–2006 indicate that the incidence of melanoma per 100,000 persons was highest in Non-Hispanic whites (26.7) followed by Hispanic whites (4.6), Hispanics (4.5), American Indian/Alaska Natives (3.3), Asian/Pacific Islanders (1.4) and blacks (1). Mortality rates, per 100,000 persons, were highest for Non-Hispanic whites (3.3), then American Indian/Alaska Natives (0.9), Hispanic whites (0.8), Hispanics (0.7), and, lastly, Asian/Pacific/Islander (0.4) and blacks (0.4).¹³ (Table 73-1) Superficial spreading melanoma was the most common histologic subtype in Non-Hispanic whites, Hispanic whites and Asian/Pacific Islander. Acral lentiginous melanoma was the most common subtype in blacks (American Indian/Alaska Native not included in analysis).¹⁴ As we can see, Non-Hispanic whites have the highest incidence and mortality rates than all of the other groups. However, if we look at stage at diagnosis and 5 year survival rates, we see that 34% of blacks present with regional or distant stages compared to 12% in whites and blacks have a 77.7% 5 year survival compared with 92.9% in whites.¹³ Limited data are available for other skin cancers, as they relate to race/ethnicity. Available statistics are shown in Table 73-2. We will now turn to the NAMC and NHANES studies.

The NAMCS study is conducted by the federal government, and looks at data for the primary diagnosis for patients visiting non-federal dermatologists. Data from the NAMCS studies revealed that some type of acne was the number one primary diagnosis in all racial groups except American Indian/Alaska Natives (Table 73-3). Other skin conditions found by race and ethnicity may be found in Table 73-3.

A second large prevalence dataset is the NHANES study. A dermatologic component to the study was carried out in the 1971–1974 period. Data for race/ethnicity were

TABLE 73-1—Melanoma of the Skin (2002–2006)

Race/Ethnicity	Prevalence	Incidence	Mortality
White	729,213	22.9	3.0
Hispanic	N/A	4.6	0.8
Non-Hispanic	N/A	26.7	3.3
Black	2,570	1	0.4
Asian/PI	N/A	1.4	0.4
AI/AN	N/A	3.3	0.9
Hispanic	N/A	4.5	0.7

(Adapted from Horner MJ, Ries LAG, Krapcho M, Neyman N, et al. SEER Cancer Statistics Review, 1975–2006. Bethesda, MD : National Cancer Institute, 2009.)

TABLE 73-2—Age-adjusted Incidence and Mortality Rates of Skin Disease by Race/Ethnic Group (2002–2006)

Race/ Ethnicity	Kaposi Sarcoma		Non-Hodgkins Lymphoma*	
	Incidence	Mortality	Incidence	Mortality
White	0.6	N/A	20.4	7.4
Hispanic	0.6	N/A	17.1	5.6
Non-Hispanic	0.9	N/A	20.9	7.5
Black	1.3	N/A	14.8	5.0
Asian/PI	0.2	N/A	12.9	4.4
AI/AN	N/A	N/A	10.8	3.6
Hispanic	0.9	N/A	16.7	5.4

*Incidences for Non-Hodgkins Lymphoma includes non-cutaneous variants

(Adapted from Horner MJ, Ries LAG, Krapcho M, Neyman N et al. *SEER Cancer Statistics Review, 1975–2006*. Bethesda, MD : National Cancer Institute, 2009.)

recorded as white, black, or other during their assessments, with Hispanic/Latinos categorized as white. 16,351 patients were classified as white, 4,163 were black, and 235 were other. The top five conditions for whites in decreasing order were: (1) acne vulgaris (2) dermatophytosis (3) seborrheic dermatitis (4) atopic dermatitis and (5) psoriasis. For blacks they were: (1) dermatophytosis (2) acne vulgaris (3) seborrheic dermatitis (4) atopic dermatitis and (5) ichthyosis/keratosis. For “other” they were: (1) dermatophytosis (2) acne vulgaris (3) atopic dermatitis (4) seborrheic dermatitis (5) verruca vulgaris. (15) The NHANES data are more of historical interest, for they do not stratify patients according to current race and ethnic groups, they do not represent current race and ethnic changes and they preceded managed healthcare.

The last source of epidemiologic data comes from the practices of academic and private dermatologists. The sources of patients, referral patterns, aggregation of data from different dermatologists, and over or underreporting are areas of discrepancies when viewing these studies. An overview of all academic and private surveys of diseases in ethnic skin are beyond our scope; however, detailed information may be found elsewhere^{15–17} We will briefly highlight unique diseases in different ethnic groups, from selected surveys, below.

We will first look at dermatologic entities seen in blacks. Hazen in 1935,¹⁸ reported that diseases occurring “more frequently in the Negro than in the white race are as follows: chloasma, cicatrix, permatitis papillaris capillitii, dermatosis papulosa nigra, dermatitis vegetans, erythema ab igne, fibroma, granuloma inguinale, tinea tonsurans, keloid, pellagra, pityriasis corporis, pityriasis faciei, pyoderma, scabies, miliary lupoid (tuberculosis), tuberculosis lichen and vitiligo. Kenney et al., 1961¹⁹, found certain “dermatoses peculiar to Negroes,” including: (1) pigmentary changes (2) dermatosis papulosa nigra (DPN) (3) pseudofolliculitis barbae (4) dermatitis papillaris nigra (acne

keloidal nuchae) and (5) perifolliculitis capitis abscedens et suffodiens (dissecting cellulitis of the scalp). Halder et al., 1983,²⁰ found greater proportions of blacks seeking care for pigmentary disorders, alopecia, and keloids. We may also add acral lentiginous melanoma as occurring more often in blacks.

Asians are known to have the following conditions occur more often: melasma, post-inflammatory pigmentation, lichen amyloidosis, photodamage (as dyspigmentation or wrinkling), alopecia, and eczema (in children).¹⁷

Hispanics/Latinos experience the following conditions with greater frequency: Hermansky-Pudlak syndrome, erythema dyschromicum perstans (ashy dermatosis), melasma, post-inflammatory hyperpigmentation, pigmented basal cell carcinoma.¹⁷ Melanoma has also been on the rise in this population, as alluded to above.

Lastly, Native Americans have been reported to have increased presentations of the following cutaneous diseases: photodermatoses (including hereditary polymorphic light eruption or actinic prurigo), collagen vascular disease (systemic sclerosis) and acanthosis nigricans (perhaps secondary to diabetes mellitus).¹⁷ However, large scale epidemiologic studies on Native Americans are lacking, and information comes from small case reports.

DISPARITIES IN HEALTHCARE, CLINICAL RESEARCH, AND HEALTH INSURANCE

To begin this section, we must define what we mean by healthcare disparities. The definition of “healthcare”, by the Institute of Medicine (IOM), is “the continuum of services provided in traditional healthcare settings, including public and private clinics, hospitals, community health centers, nursing homes, and other healthcare facilities, as well as home-based care.” The IOM further defines “disparities in healthcare” as “racial or ethnic differences in the quality of healthcare that are not attributed to access-related factors

TABLE 73-3—National Ambulatory Care Survey (NAMCS) – 1993-2002 – Top 10 Primary Diagnoses by Racial/Ethnic Group for Non-Federal Dermatologists in the United States

White	Black	Asian	Native Hawaiian/Pacific Islander	Hispanic or Latino	American Indian/Alaska Native
Other acne	Other acne	Other acne	Other acne	Other acne	Viral warts, unspecified
Actinic keratosis	Unspecified cause	Unspecified cause	Other seborrheic keratosis	Unspecified cause	Rosacea
Viral warts, unspecified	Seborrheic dermatitis, unspecified	Benign neoplasm of skin, site unspecified	Acne	Acne	Scabies
Unspecified cause	Other atopic dermatitis and related conditions	Other atopic dermatitis and related condition	Viral warts, unspecified	Other psoriasis	-
Malignant Neoplasm of skin, site unspecified	Acne	Other psoriasis	Sebaceous cyst	Viral warts, unspecified	-
Benign neoplasm of skin, site unspecified	Other psoriasis	Viral warts, unspecified	Other atopic dermatitis and related condition	Sebaceous cyst	-
Other psoriasis	Alopecia, unspecified	Other seborrheic keratosis	Dermatophytosis of nail	Psoriasis	-
Acne	Noncodable diagnosis/insufficient for coding	Urticaria, unspecified	Malignant neoplasm of skin of other and unspecified parts of face	Actinic keratosis	-
Other seborrheic keratosis	Keloid scar	Acne	Unspecified cause	Benign neoplasm of skin, site unspecified	
Eczema	Viral warts, unspecified	Sebaceous cyst	Lichenification and lichen simplex chronicus	Alopecia areata	-

(Adapted from Taylor SC, Summers P. Defining Skin of Color. In: Kelly AP, Taylor SC, editors. *Dermatology for Skin of Color*. New York: McGraw-Hill; 2009. 8–15.)

or clinical needs, preferences, and appropriateness of intervention.”²¹ However, the Agency for Healthcare Research and Quality (AHRQ) of the U.S. Department of Health and Human Services recognizes that there isn’t a consensus on the definition in their National Healthcare Disparities Report (2003).

Five theories have been proposed that may explain why certain racial/ethnic groups experience disease and healthcare differently. They are the racial-genetic model, the health-behavior model, the socioeconomic status (SES) model, the psychosocial stress model, and the structural-constructivist model. Briefly, the racial-genetic model states that inherent genetic factors in racial groups may account for differences in disease manifestations. The health-behavior model states that voluntary behaviors, adapted by certain groups, leads to perceived differences in health (e.g., high caloric intake and low physical activity). The

SES model believes that research is confounded by social and economic factors, related to income, poverty, and access to health insurance. The psychosocial stress model was proposed after the SES model failed to completely account for healthcare disparities. It states that stresses associated with institutional and interpersonal racism may be the root of disparities. Lastly, the structural-constructivist model, although unclear, attempts to view racism as a dual entity. The structural component is the constraint of individuals by external social structures, created by the shared and distributed expectations of others. The constructivist aspect is the construction of a cognitive representation of the reality of life out of an amalgam of socially shared understandings distributed within a society. Although one theory does not fully account for the totality of disparities, these concepts have been used in public health research.²² These concepts have also become

a focus of the federal government, to further understand and possibly eliminate healthcare disparities, which we will examine below.

Within the realm of clinical research, the National Institutes of Health (NIH) Revitalization Act of 1993 (PL 103–43) was passed, which required the creation of guidelines for the inclusion of women and minorities (and their subpopulations) in research. These guidelines, published in 1994 and amended in 2000, cover all biomedical and behavioral research involving human subjects (including clinical trials), supported by the NIH. The guidelines affect all age groups, with inclusion of women and minorities mandated, regardless of cost.²³

The United States Congress, realizing differences in healthcare in minority groups through clinical research, established the Healthcare and Quality Act (Public Law 106–129) in 1999. The act commissioned the IOM and the AHRQ to develop reports on the disparities in healthcare delivery in minority groups in 2003. The AHRQ was further instructed to report progress on healthcare disparities, annually, in the National Healthcare Disparities Report (NHDR). We will first look at U.S. census data and then examine the 2008 version of the NHDR.

The U.S. Census Bureau, in their 2008 Income, Poverty, and Health Insurance report, found that blacks had the lowest median income (\$34,218) compared to all other racial and ethnic groups, in 2008. Hispanics had the second lowest median income, making \$37,913 in 2008. The median incomes for blacks and Hispanics were 62% and 68% of Non-Hispanic whites, respectively. Asians had greater median income, \$65,637, as compared to Non-Hispanic whites (\$55,530). In terms of poverty, blacks had the highest rates of poverty (24.7%, 9.4 million individuals), followed by Hispanics (23.2%, 11 million), Asians (11.6%, 1.6 million), and Non-Hispanic whites (8.6%, 17 million). Lastly, the uninsured rate was highest for Hispanics (30.7%, 14.6 million), then blacks (19.1%, 7.3 million), Asians (17.6%, 2.3 million), and Non-Hispanic whites (10.8%, 21.3 million). From the above data we can discern that blacks and Hispanics have the lowest median incomes, greatest rate of poverty, and highest rates of being uninsured.

The 2008 NHDR, although, not specifically addressing dermatologic disease, did report on disparities in access to medical care, and disproportionate burden of diseases that may affect dermatologic care. Blacks had a 9.4 times greater rate of new AIDS cases, greater rate of lower extremity amputations in diabetics, and lack of prenatal care in the 1st trimester as compared with whites. Asians had issues with timeliness of care, while American Indians and Alaska Natives experienced differences in prenatal care and colorectal cancer screening. Hispanics also experienced a higher proportion of new AIDS cases, as compared to whites. Lastly, poor individuals were more likely to have communication disparities with their provider and have a greater proportion of patients with delay in care.²⁴

Within the field of dermatology, specifically as it relates to skin of color, there is dearth of quality scientific data in the form of blinded trials, especially regarding structural and functional differences between ethnic groups. As well, there is a severe lack of randomized controlled trials for evaluation of skin diseases and their treatment in skin of color. Many published reports of treatments of dermatologic diseases in skin of color are anecdotal and lack necessary scrutiny in their evaluation. At a meeting of the National Institutes of Arthritis and Musculoskeletal Disease and Skin Disease (NIAMS) in 2000, on healthcare disparities in dermatology, Taylor stated that:

A review of the literature reveals a marked paucity of basic science research on skin of color. Many of the basic science research studies involving the structure of skin of color (e.g., those aimed at understanding the human cutaneous appendages such as the apocrine gland) date back to the early part of this century. They involve small numbers of subjects, and were not blinded. This inadequate research base regarding skin of color highlights the need for blinded, scientific investigations involving larger numbers of subjects from each of the various racial groups.²⁵

This lack of basic data makes inferences about racial differences in presentation of skin and hair disorders infirm. Additionally, formulation of treatments for ethnic skin disorders may be hindered, because of poor quality of foundational data.

With regard to a lack of basic science, randomized clinical, and epidemiologic research involving those with skin of color, the NIAMS has outlined a strategic research plan to reduce and eventually eliminate healthcare disparities as they relate to rheumatologic and dermatologic disease. They have indicated research priorities for five diseases: (1) lupus (2) scleroderma (3) osteoarthritis (4) vitiligo and (5) keloids. They acknowledge that these entities affect one or more racial and ethnic minorities with greater frequency, earlier, or with greater severity than whites.²⁶ In their report, they state that African American women have a three times higher incidence and mortality, earlier presentation and more serious complications with lupus than white women. They further state that nine times more women than men have lupus, and that lupus is also more common in women of Hispanic, Asian, and Native American descent. With regards to scleroderma, they report that while it affects members of all ethnic groups, it is particularly prevalent in certain Native American people, with a genetic susceptibility site identified in Choctaw Native Americans of Oklahoma. Although vitiligo affects all racial and ethnic groups, they state that psychologic and social consequences are particularly profound in people of color. Lastly, they recognize that keloids are seen predominantly in African American individuals.²⁶

In terms of skin cancer, we have seen, as alluded to in the SEER data in the last section, that those of darker

pigment have lower rates of developing invasive melanoma as compared with Non-Hispanic whites. However, those individuals that do develop invasive melanoma tend to do worse than their Non-Hispanic white counterparts (more advanced stage at diagnosis and worse 5-year survival rate). Suggested causes may be advanced stage at diagnosis, increased rates of melanoma in non-sun-exposed sites, a more aggressive form of disease, lack of adequate skin cancer education, decreased use of sun protection, decreased likelihood to undergo full body skin examination and language barriers.²⁷

Even with greater federal emphasis placed on reducing healthcare disparities, in both research and clinical settings, recruitment of racial and ethnic minorities has proven difficult.²⁸⁻³⁰ This may stem from medical mistrust, lack of transportation, need for child care, loss of income when seeing a physician, communication barriers, cultural barriers, misperceptions, or lack of legal immigration status. Furthermore, lack of use or nonuniform use of racial and ethnic descriptors in the scientific literature also presents challenges when interpreting data from basic and clinical research.

From our discussion, we may glean that there are healthcare disparities amongst racial and ethnic groups that cannot be accounted for by socioeconomic status alone. Efforts have been made by the NIH and federal government to identify, understand, and ramify those differences. This requires the use of language interpreters, improvement of cultural sensitivity of physicians, increase in the number of minority researchers and clinicians, community-based outreach programs and creation of large, current datasets examining the burden of skin disease, especially amongst those of color. We will now turn to a discussion of structural and functional differences in Skin of Color.

BRIEF OVERVIEW OF STRUCTURAL AND FUNCTIONAL DIFFERENCES OF SKIN OF COLOR

Studies investigating skin and hair structure and function in various ethnic groups have revealed interesting differences in the epidermis, dermis, and hair follicles. It is our objective to briefly examine those differences, in that order. As we proceed, keep in mind that research on ethnic skin differences has been done on small sample sizes, with sometimes conflicting results. Although we will highlight certain differences, more research needs to be done to confirm those relationships. A summary of the findings is shown in Table 73-4.

Epidermis

The epidermis is divided into five layers: (1) stratum corneum (2) stratum lucidum (3) stratum granulosum (4) stratum spinosum and (5) stratum basale. There are

four main cell types in the epidermis: (1) keratinocytes (2) melanocytes (3) Langerhans cells and (4) Merkel cells. We will begin by describing differences in the stratum corneum and then proceed to differences in melanocyte/melanosome structure and function.

Various properties of the stratum corneum have been examined in ethnic skin, including the number of cell layers, corneocyte size, phenotype and desquamation, lipid content, barrier function (transepidermal water loss), water content, pH, and microflora.

Black skin may have more corneocyte cell layers than white patients, as evidenced by greater number of tape stripplings (21.8 vs. 16.7 stripplings).³¹ However, there has been no demonstrable difference in the thickness of the stratum corneum between blacks and whites, which may be secondary to increased cohesiveness of the cells in the stratum corneum.³¹

There have been no differences found for both corneocyte size and maturation between blacks, whites, and Asians. The desquamation rate, lipid content, barrier function (transepidermal water loss), and water content between blacks, whites, Asians, and Hispanics has shown conflicting results, depending on the study.³²

Blacks have been found to have a lower skin pH after three skin stripplings than whites, and blacks have lower pH on their cheeks than whites. Blacks have also been found to have increased numbers of *Candida albicans* (150%) and anaerobic bacteria (650%) on their skin than whites.³²

We will now turn to differences in the pigmentation between those of dark skin and those of fair skin. It has been shown that the number of melanocytes does not differ amongst racial groups.³³ However, observable differences are attributed to differences in melanosome number, size, aggregation, number in the basal layer, distribution, and total melanin content.

Blacks have a greater number of melanosomes in the epidermis than whites. Melanosomes are also larger and denser in blacks compared with whites. Darker-skinned blacks tend to have their melanosomes distributed as closely packed doublets, residing mostly in the basal layer, with a decreasing melanosome gradient as we travel up the stratum corneum. Fair-skinned whites have smaller and less melanosomes, which tend to be aggregated and located mainly in the stratum corneum, with less melanosomes in the basal layer than blacks. This can vary with lighter-skinned blacks and darker-skinned whites, which show intermediate features between dark-skinned blacks and fair-skinned whites. In addition to these epidermal differences, we will now examine differences in dermal structure.

Dermis

The dermis is divided into the upper papillary and the deeper reticular dermis. Cells that reside within the dermis include fibroblasts, macrophages, mast cells, and

TABLE 73-4—Differences in Structural and Functional Characteristics of Ethnic Skin

	Blacks (Darker skinned)	Whites (Fair skinned)	Asians	Hispanics
Epidermis				
Corneocyte Surface Area	911 μm^2	899 μm^2	909 μm^2	
Stratum corneum thickness	5-19.1 μm	5-19.1 μm		
Stratum corneum Layers	21.8 cell layers	16.7 cell layers		
Spontaneous Desquamation	?	?	?	
Transepidermal Water Loss (TEWL)	?	?	?	?
Conductance Stratum Corneum Lipid Content	Higher ?	Lower ?	?	Higher ?
Dryness Eumelanin: Pheomelanin	Higher Highest	Lower Lowest	Intermediate (East Indians)	
Melanocyte number	No significant difference (1054 melanocytes/ mm^2)	No significant difference (1241 melanocytes/ mm^2)		
Gene Expression of Tyrosinase	No significant difference	No significant difference		
Melanosomes	1. >200 melanosomes 2. Located mostly in basal layer 3. Larger, more oval, denser 4. No limiting membrane 5. Closely packed doublets 6. Degrade slower 7. Distribute throughout entire epidermis Greater	1. < 20 melanosomes 2. Located mostly in stratum corneum 3. Smaller, less oval, less dense 4. Limited membrane 5. Aggregated with spaces between them 6. Degraded faster Lesser	1. Aggregated and more compact than Whites 2. Fewer basal cell melanosomes	
Total Melanin Content				
Dermis				
	1. Thicker 2. More compact 3. Less distinct papillary and reticular layers 4. Loosely stacked, smaller collagen fiber bundles	1. Thinner 2. Less compact 3. More distinct papillary and reticular layers 4. Larger collagen fiber bundles		
Melanophages	Larger			
Fibroblasts	1. Larger 2. More biosynthetic organelles 3. More multinucleated			
Mast Cells	1. Larger granules 2. 15% more parallel-linear striations	1. Smaller granules 2. 30% more curved lamellae 3. Tryptase reactivity confined to peripheral area of granules		
Nerve Fiber Network Elasticity	No significant difference ?	No significant difference ?		?
Cutaneous Appendages				
Sebaceous Glands	Larger, greater sebum production	Smaller, less sebum production		
Apocrine Glands	Larger, greater number, more fluid secretion	Smaller, less numerous, less fluid secretion		
Mixed Apocrine-Eccrine Glands	More	Less		

(Continued)

TABLE 73-4—Differences in Structural and Functional Characteristics of Ethnic Skin (Continued)

	Blacks (Darker skinned)	Whites (Fair skinned)	Asians	Hispanics
Eccrine Glands Hair	No significant difference 1. Elliptical cross section 2. Twisted oval rod fiber shape with flattening 3. Variable diameter 4. Less tensile strength (breaks more easily) 5. 0.6 follicular units/mm ² 6. 3 hairs/follicular unit 7. Less moisture 8. Less anchoring elastic fibers	No significant difference 1. Intermediate cross section 2. Cylindric fiber shape 3. Intermediate diameter 4. More tensile strength (similar to Asians) 5. 1 follicular unit/mm ² 6. 2 hairs/follicular unit 7. More moisture	1. Round cross section 2. Cylindric fiber shape 3. Largest diameter 4. More tensile strength (similar to Whites) 5. 1 follicular unit/mm ² 6. 2 hairs /follicular unit	

"?" = data available, but inconclusive; Empty cell = data not available.

(Adapted from Oresajo CO, Pillai S, Richards GM. Structure and Function of Skin and Hair in Pigmented Races. In: Halder RM, editor. *Dermatology and Dermatological Therapy of Pigmented Skins*. New York: Taylor and Francis; 2006, p. 3–16.)

circulating immune cells. The dermal matrix is composed of collagen (produced by fibroblasts), elastic fibrous tissue, and “ground substance” (glycoproteins, proteoglycans, and glycosaminoglycans). We will look at differences in these structures as they relate to race and ethnicity.

The dermis of blacks has been found to be thicker and more compact than that of whites.³⁴ The differentiation of the papillary and reticular dermis is more difficult in blacks as compared to whites. Blacks have loosely-stacked, smaller collagen fiber bundles and many collagen fibrils and glycoprotein fragments, while whites have more distinct papillary and reticular dermal structures, larger collagen fiber bundles, and occasional fiber fragments.³² The fibroblasts in blacks are larger and are more multinucleated than whites.³² The mast cell number and size have not been found to be different between races; however, blacks do have larger mast cell granules than whites.³² Lastly, there does not seem to be an appreciable difference in the nerve fiber network and there are conflicting results relating to elasticity of the dermis.³²

Cutaneous Appendages

Cutaneous appendages are derivatives that include sebaceous glands, sweat glands, and hair, amongst others. Sweat glands may be further divided into apocrine (develop at puberty and found in axillae, anogenital area, face, scalp, external auditory canal, and mammary glands), eccrine (found all over body, especially palms and soles), and apocrine glands (develop at puberty, axillae only).

Beginning with the sebaceous glands, we find that blacks have larger and more productive glands than whites.³² Second, apocrine glands have been found to be larger, greater in number, and more productive in blacks compared to whites.³² Third, there has been no difference found between races for eccrine glands.³² Lastly, black skin has been found to have more apocrine sweat glands than whites.³²

When considering hair from different races, we notice that blacks, although having no differences in chemical composition, show interesting structural differences from whites and Asians when looking at hair cross section, fiber shape, diameter, tensile strength, distribution, moisture, and anchoring.³⁵

When examining hair cross-sections, we notice that blacks have an elliptical shape, while Asians have more of a round shape, and whites intermediate between the two. Hair fibers appear as a twisted oval rod with pronounced flattening in blacks and cylindric in whites and Asians. The hair diameter is greatest in Asians, intermediate in whites, and variable in blacks. Black hair seems to have less tensile strength as compared with whites and Asians, perhaps leading to more breakage. Additionally, blacks have, on average, less follicular units per square millimeter than whites or Asians, but tend to have more hair per follicular unit. Lastly, blacks tend to have less hair moisture and less elastic fibers anchoring the hair in place than whites.³⁵

OVERVIEW OF CUTANEOUS REACTION PATTERNS OF SKIN OF COLOR

From the above discussion, we see that differences exist in skin structure, which translate into differences in function and responses to the physical environment. These differences may be understood as cutaneous reaction patterns in those with darker skin pigmentation. A study of reaction patterns alleviates the need to discuss all skin diseases that manifest differently in darker skin, while providing a basis with which to understand them all. Although various classifications of cutaneous reactions in dark skin exist, we will focus on three predominant patterns, first proposed by Brauner³⁶ and modified by Andersen and Maibach,³⁷ with representative examples. These include: (1) pigment lability (hyper- or hypopigmentation) (2) mesenchymal responses (fibromatosus and granulomatous) and (3) follicular responses.

Pigment Lability

In order to understand pigment lability, we must first define the term. We will use the definitions of Nordlund et al. to differentiate between two different types of chromophores – defined as all chemicals and structural items that impart color to the skin. “Pigment” will be used to describe “melanotic” chromophores (relating to the melanocytes and melanin), differentiating them from those chromophores composing other elements of the skin, which include hemoglobin, carotenes and collagen.³⁸ Lability, as defined by the Merriam-Webster dictionary, means readily or continually undergoing chemical,

physical, or biologic change or breakdown (unstable).³⁹ Therefore, pigment lability will refer to the instability of the melanocytic system in response to internal and external stimuli, with deviations from the normal manifesting as hyperpigmentation, hypopigmentation, or depigmentation. Hyperpigmentation may occur because of increased melanin production (hypermelanosis) or number of melanocytes (hypermelanocytosis). The melanin may be distributed to the epidermis, dermis, or both. Similarly, hypopigmentation is caused by the decreased number of melanocytes, or decreased melanin production, melanosome biogenesis, transport, and transfer.³⁸ Representative entities, among darker-skinned individuals, include

What We Know

- Despite the limitations of the concept of race, divisions along racial lines continue to enter clinical research because of their use by the federal government.
- Epidemiologic data on skin diseases, especially as they relate to different ethnic groups, is limited. However, from the available data for malignant melanoma, we may discern that, although, Non-Hispanic whites have the highest incidence and mortality rates than all of the other groups, blacks have a more advanced disease presentation and poorer 5-year survival rate than whites. Also, in terms of melanoma incidence, Hispanic whites and Hispanics follow Non-Hispanic whites, per 100,000 persons. Alaskan/Pacific Islanders follow Non-Hispanic whites in regards to melanoma mortality rates.
- From the available data, we may say that there are certain dermatologic conditions that are found with greater frequency in certain ethnic groups. Blacks have an increased frequency of pigmentary disorders, alopecia, keloids, dermatosis papulosa nigra, and acne keloidalis nuchae. Asians present more frequently with pigmentary disorders, eczema, lichen amyloidosis, and photodamage. Hispanics frequently display pigmentary disorders, erythema chromatium perstans, and increased rates of melanoma. Native Americans may show greater presentations of photodermatoses, collagen vascular diseases, and acanthosis compared with other races. However, large studies on the incidence, prevalence, and morbidity of dermatologic diseases in the various ethnic groups are needed in order to further clarify these relationships.
- Five theories to explain healthcare disparities include: (1) racial-genetic model (2) health-behavior model (3) socioeconomic status model (4) psychosocial stress model and (5) structural-constructivist model.
- Healthcare disparities, found to exist by the federal government, led to the development of the NIH revitalization act of 1993 (inclusion of women and minorities in all biomedical research supported by NIH) and the Healthcare and Quality Act of 1999 (commissioned AHRQ to develop annual healthcare disparities reports from 2003).
- Blacks and Hispanics have the lowest median incomes, greatest rates of poverty, and highest rates of being uninsured, according to the 2008 U.S. Census report.
- There is a lack of quality basic science and clinical dermatologic research in those with skin of color. Increased recruitment of minority groups is needed in randomized controlled trials to ensure equality of access to treatment and extrapolation of research to all groups.
- The National Institutes of Arthritis and Musculoskeletal Diseases and Skin proposed a plan to reduce healthcare disparities in five disease categories: (1) lupus (2) scleroderma (3) osteoarthritis (4) vitiligo and (5) keloids.
- Despite federal efforts to reduce healthcare, clinical research, and health insurance disparities, recruitment of racial and ethnic minorities has proven difficult.
- Some structural differences exist in the epidermis, dermis, and cutaneous appendages of blacks compared to whites, including: (1) more corneocyte layers (2) greater number, denser, and more distributed melanosomes (3) larger, more multinucleated fibroblasts (4) larger mast cell granules (5) increased number and production of apocrine, sebaceous, and apocrine glands and (6) tightly curled, less dense, drier, less anchored hair
- Three general cutaneous reaction patterns in darker skin include: (1) pigment lability (2) mesenchymal response (fibromatous and granulomatous) and (3) follicular response

postinflammatory hyper-/hypopigmentation, vitiligo, melasma, erythema dyschromicum perstans (ashy dermatosis), congenital Mongolian spots, Nevus of Ota, Nevus of Ito, Nevus of Hori, idiopathic guttate hypomelanosis, nevus depigmentosus and pityriasis alba

Mesenchymal Response

The second predominant reaction pattern of darker skin types is the mesenchymal response, which includes both the fibromatous and granulomatous reactions types. The term mesenchyme represents an embryonic precursor to connective tissue. Mesenchymal stem cells (MSC) are capable of differentiating into chondrocytes (cartilage), osteocytes (bone), tenocytes (tendon), adipocytes (fat) and myocytes (muscle). Fibroblasts are also derived from MSCs and are responsible for the production of collagen. Keloids, which represent an abnormal deposition of collagen (fibroplasia) in the dermis in response to trauma, skin tension, infection, endocrine factors and genetic factors, are found with a higher incidence (5-16 times) in black individuals.⁴⁰ This may be secondary to the larger, more nucleated fibroblasts of blacks compared to whites, mentioned above, and/or the interaction of fibroblasts with melanocytes.⁴⁰ Asians and Hispanics also seem to have an intermediate incidence of keloids as compared with blacks and whites.⁴⁰

The second type of mesenchymal response is the granulomatous reaction. Granulomas are aggregates of histiocytes that tend to occur in the dermis or subcutaneous tissue. One such granulomatous disorder that occurs with greatest frequency in blacks is sarcoidosis.⁴¹ This disease entity can have a more severe course and more extensive, variable skin manifestations in blacks.⁴¹

Follicular Response

This last reaction pattern involves a greater predilection, in those of darker skin, for the pilar apparatus. This may be because of structural differences in cutaneous appendages (sebaceous, apocrine, and apocrine glands) or hair cross section, fiber shape, diameter, tensile strength, distribution, moisture, and anchoring. Diseases that present in a follicular pattern include follicular tinea versicolor, follicular eczema, dermatosis papulosa nigra, acne keloidalis nuchae, pseudofolliculitis barbae, pomade acne, papular pityriasis rosea, papular lichen planus, secondary syphilis, perifolliculitis capitis abscedens et suffodiens, and alopecias (traction and central centrifugal cicatricial alopecia).^{42,43}

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Dermatoepidemiology and Evidence-based Dermatology Training During Residency

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Dermatoepidemiology explores dermatologic illness and its management at the population level. The simplest definition for dermatoepidemiology may be the study of “disease occurrence in a population”.¹ In order to determine prevalence of a specific skin disease, there must be defined criteria for the diagnosis of the disease. The affected population can then be studied to determine risk factors, transmission, treatment, and prevention strategies for a given disorder. Notable historic examples of dermatoepidemiology include the characterization of poxvirus, clinical patterns, seasonal appearances, expected target populations, resistance and ultimately public health intervention, and prevention with vaccination, which has led to the eradication of smallpox.² While clinical therapy treats illness to benefit the individual, dermatoepidemiology examines disease risk and whether population or environmental factors can promote preventive and treatment strategies.

Dermatoepidemiology constitutes an important foundation for dermatology training as it encompasses observation and deduction. Dermatoepidemiology includes primary prevention (health promotion and protective measures), secondary prevention (early detection and treatment), and tertiary prevention (limitation of disability).³ Clinical dermatoepidemiology tracks clinical outcomes in individual patients, and generalizes these observations to population subsets.

Understanding the principles of epidemiology is critical to an understanding of evidence-based medicine. Physicians must be able to analyze medical literature to determine the validity and applicability of conclusions relative to their patient population. In order for this to occur, residents must be trained in the language and concepts of epidemiology including the appropriate use of statistical tests and detection of confounding factors and bias. They must also be able to rate the evidence based on the study design.⁴ Most medical students receive some introduction into medical epidemiology during medical school;

however, these concepts need to be reinforced during residency. In fact, studies have shown a low level of epidemiologic knowledge among practicing physicians.⁵

The Dermatology Residency Review Committee requires that dermatology residents demonstrate knowledge of epidemiologic sciences, but there is little published on Dermatoepidemiology Education during Dermatology Residency.⁶ A notable exception is the dermatoepidemiology curriculum at Case Western Reserve University, which implemented a monthly lecture series for dermatology residents.^{7,8} The Case Western Reserve University DermatoEpidemiology curriculum was based on the Epidemiology Curriculum for Dermatologists developed by the International DermatoEpidemiology Association.^{7,9} They evaluated their curriculum and found that residents preferred interactive discussions over lecture format as well as case-based learning from the dermatology literature.

Indeed, other medical disciplines use a journal club format to teach principles of epidemiology and evidenced-based medicine.¹⁰ The Primary Medical Education program (PRIME Curriculum) at the University of California San Francisco has been particularly successful in fostering resident scholarship as part of the Internal Medicine Residency Program at UCSF.¹¹ The PRIME Curriculum consists of a didactic curriculum to reinforce key concepts of evidence-based medicine followed by weekly afternoon small group journal clubs. The PRIME Program's didactic lecture series is similar to curriculums recommended by the International DermatoEpidemiology Association and that used by Case Western Reserve University, (Table 74-1).^{7,9,11}

Dermatoepidemiology resources for dermatology resident education include the following: (1) The International Dermatoepidemiology Association, established in 1996 in order to provide resources for those interested in the epidemiology of skin disease⁹, (2) European

TABLE 74-1—Epidemiology Curriculum Comparison

International Dermatoepidemiology Association	Case Western Reserve University	PRIME Epidemiology Curriculum UCSF
Overview of Dermatoepidemiology	Overview of variables, tests and statistics	Overview of epidemiology study types
Validity	Validity and reliability of screening tests	How epidemiology data are presented
Bias in studies	Bias in studies and mortality	How to design a research question
Evidence-based medicine	Case control studies and measures of risk	Study design and sampling
No evidence of effect	Hypotheses testing, error and p-values	Issues in measurement
Case control studies	Quality of life studies	Causal inference
Quality of life studies	Systematic reviews	Qualitative biostatistics 1
Systematic reviews (Meta-analysis)	Confounding	Qualitative biostatistics 2
Defining disease(s) for a study	Health services research	Computer skills
Confounding	Randomized-controlled trials	Research ethics
Health services research		Systematic review Meta-analysis

Dermato-Epidemiology Network (EDEN), established in 1995 to improve links between European countries and further develop the role of epidemiology, clinical research, and health services research in dermatology,¹² (3) www.ebDerm.org,¹³ and (4) the Cochrane Skin Group, which prepares, maintains and disseminates systematic reviews of clinical interventions in dermatology.^{14,15} These resources help meet the obligation to ensure exposure to dermatoepidemiology—one of the vital subdisciplines of the specialty and their use will lead to increasing the relevance of epidemiology in dermatology.⁴

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http://www.acgme.org/acWebsite/downloads/RRC_progReq/081_procedural_derm_07012010_1-YR.pdf

Electronic Resources For Evidence-Based Dermatology

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This chapter contains summarized lists of useful web sites in the field of evidence-based dermatology. As our readers are familiar with many of these web sites, we avoid explicit explanations.

Available general medical search engines as well as selected evidence-based search engines, and databases are shown in Tables 75-1 and 75-2 respectively.

TABLE 75-1—General Medical Search Engines

Database	Web site	Notes
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/	Comprises over 20 million citations for biomedical literature from MEDLINE, life science journals, and online books.
EMBASE	http://www.embase.com/	Covers 2,000 biomedical titles not currently offered by MEDLINE
Scopus	http://www.scopus.com/home.url	The largest abstract and citation database of research literature and quality web sources covering nearly 18,000 titles

TABLE 75-2—Evidence-based Search Engines, and Databases

Database	Web site	Notes
The MEDION database	http://www.mediondatabase.nl/	References and abstracts of published diagnostic studies and diagnostic systematic reviews
PubMed Clinical Queries	http://www.ncbi.nlm.nih.gov/corehtml/query/static/clinical.shtml	Systematic search engines to find relevant randomized trials, systematic reviews, and genetic studies.
Trip Database	http://www.tripdatabase.com/index.html	The most comprehensive database to search for all available evidence including systematic reviews, guidelines, randomized trials, etextbooks and patient information
Cochrane Central Register of Controlled Trials (CENTRAL)	onlinelibrary.wiley.com/o/cochrane/cochrane_clcentral_articles_fs.html	Contains approximately 640,000 records of published randomized trials (updates frequently)
Cochrane Database of Systematic Reviews (Cochrane Reviews)	onlinelibrary.wiley.com/o/cochrane/cochrane_clsysrev_articles_fs.html	Consists of more than 5,000 Cochrane systematic reviews
Database of Abstracts of Reviews of Effects (DARE)	http://www.crd.york.ac.uk/CMS2Web/SearchPage.asp	Non-Cochrane systematic Reviews (more than 14000) plus Cochrane reviews. Produced by Center for Reviews and Dissemination (CRD)
Health Technology Assessments (HTA) Database	onlinelibrary.wiley.com+cochrane_clhta_articles_fs.html	Completed and ongoing health technology assessments (approximately 10000) from around the world. Produced by centreCenter for Reviews and Dissemination (CRD)
NHS Economic Evaluation Database	http://onlinelibrary.wiley.com/o/cochrane/cochrane_cleed_articles_fs.html	Systematic identification of economic evaluations from around the world and appraising their quality (approximately 30000). Produced by Center for Reviews and Dissemination (CRD)
ACP Journal Club	http://www.acpj.org	Provides summaries of selected original and review articles in the medical literature
Clinical Evidence	http://www.clinicalevidence.org	Provides current evidence-based reviews of the treatments for more than 260 conditions.

Evidence-based organizations are presented in Table 75-3.

TABLE 75-3—Evidence-based Organizations/Main Web Sites

Organization	Web site	Note
Dermatology-Related organizations		
Cochrane Skin Group	http://skin.cochrane.org/	The Cochrane Skin Group is a network of people from all over the world committed to producing and updating reviews of trials relating to skin conditions.
American Dermato-Epidemiology Network	http://www.facebook.com/group.php?gid=156000547744724 http://groups.google.com/group/adenetwork?pli=1	It was established by a group of international dermat-epidemiologists with the aim of furthering research in epidemiology and health services research in dermatology
European Dermato-Epidemiology Network	http://eden.dermis.net/eden/content/e02eden/e01aims/e01programm/index_ger.html	It is a European group aimed at: 1 improving the role of epidemiology in dermatology 2 sharing expertise 3 producing high quality work 4 contacting isolated groups and encouraging them to join in
EBDERM	http://208.106.170.94/	It was made to enhance dermatology resident education in the area of evidence-based medicine, and promote evidence-based practice through education and searching tools.
General Sites		
Center for Health Evidence	http://www.cche.net/	The Center for Health Evidence provides a range of information and communication services to a variety of health organizations and professional associations. It includes American Medical Association's "Users' Guides to the Medical Literature"
National Institute for Clinical Excellence (UK)	www.nice.org.uk	The National Institute for Health and Clinical Excellence (NICE) provides guidance, sets quality standards and manages a national database to improve people's health and prevent and treat ill health
Centre for Evidence-Based Medicine	http://www.cebm.net/index.aspx?o=1001	It was established in Oxford as the first of several UK centers with the aim of promoting evidence-based healthcare.

Table 75-4 summarizes the main databases for guidelines.

TABLE 75-4—Clinical Guidelines

Site	URL	Notes
National Guideline Clearinghouse	http://www.guidelines.gov/index.asp	Evidence-based clinical practice guidelines; sponsored by the Agency for Health Care Policy and Research, American Medical Association, and the American Association of Health Plans
CPG Infobase	http://www.cma.ca	Clinical practice guidelines produced in Canada by a medical or health organization, professional society, government agency, or expert panel
American Academy of Dermatology (AAD)	http://www.aad.org	Guidelines provided by AAD; for Dermatology (AAD) members only
British Association of Dermatology (BAD)	http://www.bad.org.uk	Guidelines by BAD; public access

Grey literature refers to a body of materials that cannot be found easily through conventional channels such as publishers. It is not a dominated resource in medical

literature but it can be valuable for some topics. Table 75-5 enlists two main sources of searching grey literature in biomedical sciences.

TABLE 75-5—Grey Literature

System for Information on Grey Literature in Europe (OpenSIGLE)	http://opensigle.inist.fr/	bibliographical references of reports and other grey literature (GL) produced in Europe until 2005
ProQuest LLC (Dissertation and theses)	http://proquest.umi.com/pqdweb?nocfc=1	700 active university publishing partners, and publish more than 60,000 new graduate works each year

A selection of dermatology online textbooks and web sites is shown in Table 75-6.

TABLE 75-6—Dermatology Online Reference Texts and Educational Material

Site	URL	Notes
EMedicine Textbook	www.emedicine.medscape.com/dermatology	Comprehensive medical online text, including sections on dermatology, emergency medicine, internal medicine, and surgery
The Electronic Textbook of Dermatology	http://www.telemedicine.org/stamford.htm	<i>Textbook of Dermatology</i> , produced by the Internet Dermatological Society
Approach to the Ddermatology Patient	http://www.angelfire.com/md2/liaquatian/Dermatology.pdf	<i>MCCQE 2000 Review Notes and Lecture Series</i>
Botanical Dermatology	http://bodd.cf.ac.uk	Online Reincarnation of Mitchell and Rook's <i>Botanical Dermatology</i>
Dermnet NZ	www.dermnetnz.org	New Zealand Dermatological Society Incorporated. Launched on March 1996
The Language of Dermatology	http://eduserv.hscer.washington.edu/dermUW/lang	Tutorial of terms used in morphologic diagnosis from the University of Washington
Virtual Hospital Site	http://www.vh.org/Providers/Lectures/PietteDermatology/BasicDermatology.html	Basic introduction to dermatology
University of Indiana— Virtual Dermatology	http://erl.pathology.iupui.edu/cases/dermcases/dermcases.cfm	Presents 20 interactive case studies for continuing medical education
Skindex	http://www.skindex.com	Website with dermatology news, articles, reviews, 5 cases for CME, and images from Thomas Fitzpatrick

The main online only dermatology journals and newsletters are mentioned in Table 75-7.

TABLE 75-7— Online Only Dermatology Journals or Newsmagazines

Journal	URL	Notes
Dermatology Online Journal	http://dermatology.cdlib.org	Peer-reviewed electronic-only journal, PubMed cited
Internet Journal of Dermatology	http://www.ispub.com/journal/the_internet_journal_of_dermatology.html	Online only journal, indexed with Google Scholar, Embase, Scopus
Dermatology Times	http://www.dermatologytimes.com	Dermatology news magazine
Cosmetic Surgery Times	http://cosmeticsurgerytimes.com	News magazine for cosmetic dermatologic surgery
Laser News	http://www.lasernews.net	Multimedia e-journal of laser dermatology

There are additional online tables that are only available on the book's web site free of charge. All tables will be updated online periodically.

FURTHER READINGS

- **Formulating a Good Research Question:**
- **AHRQ Annual Meeting** Link: <http://www.ahrq.gov/about/annualmtg08/091008slides/Lau.ppt>

- **Extra Meta-Search Engines:**

- Link: <http://www.tripdatabase.com/index.html>
- **OVID search engine** Link: <http://www.ovid.com/site/catalog/DataBase/904.jsp?top=2&mid=3&bottom=7&subsection=10>

- SUMSearch from UT Health Science Center Link: <http://sumsearch.uthscsa.edu/>
- Essential Evidence Plus Link: <http://www.essential-evidenceplus.com/>
- Primary Care Electronic Library (PCEL) University of London Link: <http://www.pcel.info/index.php?fuse=search.ebmprimer>
- Diagnostic Systematic Reviews:
 - Cochrane Handbook for Diagnostic Test Accuracy Link: <http://srdta.cochrane.org/en/authors.html>
 - Systematic Reviews of Diagnostic Tests in Cancer: Review of Methods and Reporting Link: <http://www.ncbi.nlm.nih.gov/articlerender.fcgi?tool=pubmed&pubmedid=16849365>
 - Diagnostic Systematic Reviews: A Schematic Road Map www.medepi.net/meta/guidelines/Diagnostic_Systematic_Reviews_Road_Map_V3.pdf
- Prognostic Studies/Systematic Reviews/Risk Factor Analysis:
 - Prognosis and prognostic research: what, why, and how? Link: http://www.bmjjournals.org/cgi/content/full/338/feb23_1/b375?maxtoshow=&HITS=10&hits=10&RESULTRFORMAT=&searchid=1&FIRSTINDEX=0&resourcetype=HCIT
 - Prognostic markers in cancer: the evolution of evidence from single studies to meta-analysis, and beyond. Link: <http://www.nature.com/bjc/journal/v100/n8/abs/6604999a.html>
 - PLoS Medicine: Systematic Reviews of Genetic Association Studies. Link: <http://www.plosmedicine.org/article/fetchObjectAttachment.action;jsessionid=CBA2106E0D7A53665C97549D7387060D?uri=info%3Adoi%2F10.1371%2Fjournal.pmed.1000028&representation=PDF>

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