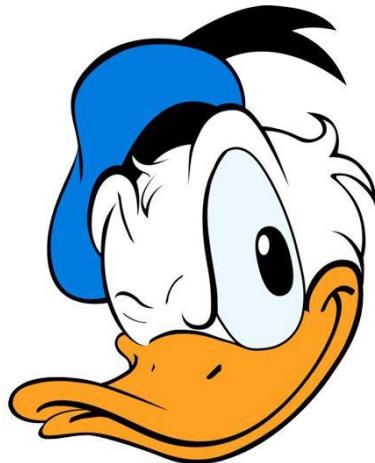


DERMATOLOGY

CME

2016





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Skin biopsy

Identifying and overcoming errors in the skin biopsy pathway

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Learning objectives

After completing this learning activity, the reader should be able to recognize the need for incorporating patient safety care initiatives relating to the skin biopsy pathway and wrong-site surgery into practice; describe the national patient safety mandates that relate to the skin biopsy pathway and wrong-site surgery; and explain how to perform a simplified version of a Healthcare Failure Mode and Effect Analysis (HFMEA) to patient care as it relates to the skin biopsy pathways and wrong-site surgery.

Disclosures

Editors

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The skin biopsy pathway involves numerous communication requirements, technical events, human handoffs, and cognitive decisions. Every step in the process has an error rate >0. To deliver the highest quality care, dermatologists obtaining skin biopsy specimens should implement systems in their office to minimize errors. This includes the prevention of wrong-site surgery, which in most instances involves accurate communication of the correct biopsy location to the performing surgeon. Part II of this continuing medical education article presents techniques for assessing and planning improvement to the skin biopsy pathway in your office, and provides a simple online quality improvement activity that allows Board-certified dermatologists the opportunity to potentially improve aspects of the skin biopsy process in their own practices, and in the process obtain Maintenance of Certification credit. (J Am Acad Dermatol 2016;74:19-25.)

INTRODUCTION

Obtaining a skin biopsy specimen is a common procedure in dermatology, and >2.2 million skin biopsy specimens are obtained annually in dermatology offices in the United States.¹ Studies indicate that the skin biopsy pathway and wrong-site surgery are common sources of error in dermatology practice, with potential patient care and legal ramifications.² Accurate communication of the correct biopsy location to the performing surgeon aids in preventing wrong-site surgery.

From the first decision to obtain a biopsy specimen until the integration of those results into the patient's care plan, it has been estimated that there are approximately 20 handoffs.² In any one of these steps, errors can occur. While the error rate occurring in any one step in the process is small, the likelihood of an entirely error-free skin biopsy process may be lower than one might think, given the large total number of steps. For example, in a 20-step pathway, if each step is 95% reliable, the overall reliability of the pathway is 36%; if the

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reliability of each step increases to 99%, the overall reliability of the pathway is 82%.² Part II of this continuing medical education article explores where errors may occur in the skin biopsy process, how to identify them in your own practice, and how to potentially address and improve them.

When errors occur, dermatologists and care teams are provided with an opportunity to reflect on their causes. Sometimes a particular event is caused by individual negligence, but often the root of the error lies in the systems and processes that should have been in place to serve as safeguards. By improving systems of care in one's office, the likelihood of errors occurring can be decreased. A number of national organizations have highlighted the importance of this process of developing, achieving, and regularly measuring a local "culture of safety."³⁻⁹ This focuses on identifying and addressing systems issues that lead individuals to engage in unsafe behaviors while maintaining individual accountability by establishing zero tolerance for reckless behavior.¹⁰ In many dermatology practices, systems may not actually be in place to detect or report errors in the first place. The first and most fundamental step in quality improvement is acknowledging that errors do occur and creating a culture and system for effective reporting of them.

HEALTH CARE FAILURE MODE AND EFFECT ANALYSIS

Key points

- "Failure mode" refers to anything that can go wrong during a single step of a multistep process
- Health care failure mode and effect analysis uses a local health care team to brainstorm ways in which things can and do go wrong in common procedures
- Hazard analysis is performed to prioritize which failure mode should be addressed first

Analyzing the possible cause of any error is important, but for many in health care it is unfamiliar. When errors occur, dermatologists must try to avoid the blame and shame mindset—"If it wasn't my fault, it must have been your fault"—and instead explore in greater detail the steps of the process to determine where and why an error occurred. To help identify and better attribute causes of error, medicine has adopted and modified an analytic strategy from industry called failure mode and effect analysis (FMEA).

FMEA is a prospective and systematic approach to identify and understand contributing factors, causes, and effects of potential failures on a process, system, or practice.¹¹ It was developed by the US military¹²

Table I. The 5 steps of health care failure mode and effect analysis

Step 1	Define the topic
Step 2	Assemble the team
Step 3	Graphically describe the process
Step 4	Conduct a hazard analysis
Step 5	Actions and outcome measures

Table II. Interpreting failure mode terminology in the process of obtaining a skin biopsy specimen

Terminology	Example
Failure of a process	Skin biopsy error occurs
Failure mode	Biopsy performed on the wrong location Inadequate specimen obtained Dermatologist never received pathology report Results never given to patient
Causes of a failure	Biopsy site not clearly marked for provider delegated to perform procedure Incorrect biopsy technique chosen Pathology report misplaced in the office Patient phone was busy 3 times, staff never tried to call them back
Effects of a failure	Treatment implemented for incorrect diagnosis Patient treated for actinic keratosis instead of invasive squamous cell carcinoma Patient does not receive biopsy results Surgery performed on wrong site

and has been in use since the 1960s in high-risk engineering industries, such as the aerospace industry.¹¹ For example, FMEA looks at the design of each piece of a jet engine, determines the impact of the failure of 1 engine subcomponent on the function of the whole engine, estimates the probability and overall severity of the failure, and then recommends design fixes to mitigate the risk of subcomponent failures that could lead to major or catastrophic engine failures.

Health care failure mode and effect analysis (HFMEA), a modified variant of FMEA, is a validated risk analysis method developed by the Veterans Administration (VA) National Center for Patient Safety in 2001. It combines features of FMEA from engineering and industry along with hazard analysis and critical control point—an assessment process developed by the US Food and Drug Administration to ensure food safety—and the VA's root cause analysis program.¹³

HFMEA is a 5-step process (Table I) that uses a multidisciplinary team to proactively evaluate a health

Table III. The skin biopsy pathway

Process step 1	Decision to perform a biopsy is made
↓	
Process step 2	Reason(s) for obtaining biopsy and risks are discussed with patient; informed consent is obtained
↓	
Process step 3	Biopsy details are determined: type and size of biopsy, no. of biopsies to obtain, body site or sites and location within lesion(s), and transport media
↓	
Process step 4	Surgical space, equipment, supplies and staff are assembled, and transport media/containers and requisition forms are obtained, labeled, and completed
↓	
Process step 5	Biopsy specimen(s) is/are obtained and placed into correctly labeled specimen container(s)
↓	
Process step 6	Methods for documenting biopsy location(s) are performed, especially if skin cancer is suspected to prevent wrong-site surgery
↓	
Process step 7	A dressing is applied and aftercare is explained to the patient
↓	
Process step 8	Details of biopsy performance are documented
↓	
Process step 9	Communication/transportation pathway for biopsy specimen(s) and requisition form(s) from surgical space to dermatopathology laboratory is engaged
↓	
Process step 10	Dermatopathology laboratory performs diagnostic techniques using specimen(s) and a pathology report is generated
↓	
Process step 11	The pathology report is transmitted to the clinician who obtained the biopsy specimen
↓	
Process step 12	The clinician determines a course of action/therapy for the patient based on the pathology report results
↓	
Process step 13	

Continued

Table III. Cont'd

The pathology report results and proposed course of action/therapy are communicated to the patient and any additional clinicians who will need this information. If skin cancer has been identified and another clinician will be performing the definitive surgery, the methods of biopsy site documentation are transmitted
↓
Process step 14
Treatment of disease is initiated based on the pathology report results

care process.¹³ It is designed for use with health care processes that have high vulnerabilities and potential for impacting patient safety.¹² Given that HFMEA has been introduced into health care in recent years, some of the terminology may be unfamiliar. Failure of a process refers to any malfunction, error, or defect that results in a process not performing as intended or not meeting desired requirements or standards. Failure mode refers to anything that could go wrong during the completion of a step in that process.¹⁴ Causes of a failure include all possible mechanisms or means that result in the failure mode, and the effects of a failure typically include the results to the end user or customer from the failure mode. Examples of these terms relevant to the process of obtaining a skin biopsy specimen can be found in Table II. HFMEA has been applied successfully to processes in a number of areas within medicine, including blood transfusion administration, surgical instrument sterilization, medication administration on oncology wards and intensive care units, ordering magnetic resonance imaging scans for patients, and others,¹⁵⁻²⁰ but it has not yet been applied in dermatology. In these other fields, applying HFMEA principles has led to reduced errors, the recognition of previously unidentified systems errors, and in some cases, improved mortality. Specific studies analyzing exact cost savings (beyond theoretical) or efficiency gains have not been completed, to our knowledge. In the remainder of this article, we will use key concepts from the HFMEA process to describe an approach to completing a quality improvement activity relating to the skin biopsy pathway.

APPLYING QUALITY IMPROVEMENT PRINCIPLES TO THE SKIN BIOPSY PATHWAY

Key points

- All steps in the local skin biopsy pathway should be defined and understood before deciding on how to improve the pathway

Table IV. Subprocesses in the skin biopsy pathway process (step 6)

Process step 6	Subprocesses
Methods for documenting biopsy location(s) are performed, especially if skin cancer is suspected to prevent wrong-site surgery	Decision is made to document location Type of documentation is chosen Documentation method is performed Result is labeled Result is stored and/or transmitted to future surgeon

- **Resources are limited, so it is important to prioritize which steps would be most important to improve**
- **Interval remeasurement is important to determine progress during a quality improvement activity**

Step 1: Define the topic

The topic of an HFMEA assessment should be a health care process that is vulnerable to error and has the potential for impacting patient safety.¹² This article will address the skin biopsy pathway.

Step 2: Assemble the team

To maximize success, the quality improvement (QI) process should be performed locally, such as in a private office, dermatology practice, department, or institution. If using classic HFMEA methods, the team would ideally include 6 to 8 multidisciplinary members who are involved in the process being analyzed and include at least a few who are considered subject matter experts.¹² For dermatology practices, assembling such a large team is often not practical, and team composition would necessarily vary. A smaller number of individuals involved in the skin biopsy pathway, such as the dermatologist and medical assistant staff, could comprise an appropriate team for office-based QI. When participating for Maintenance of Certification (MOC) credit, the dermatologist is the only required participant. Other team members may bring perspectives unknown to the dermatologist, so forming even a small team to review these perspectives is encouraged. Consideration could even be given to including the patient's perspective into the quality improvement process, especially when the process to be improved involves the patient's experience of care. This has been done in other HFMEA processes in other fields.¹⁷

Step 3: Review and describe the process

The entire process to be analyzed should first be described in a flow diagram. This is usually performed in a "brainstorming" fashion. As a group, the team slowly clarifies all the steps involved in the

process from start to finish. An example of a flow diagram for the main process steps in the skin biopsy pathway created by the authors is found in Table III. Next, subprocesses within each main process step are identified in a similar manner. For example, subprocess steps contained within skin biopsy pathway process number 6 are presented in Table IV.

Step 4: Prioritize which aspect of the pathway to improve

Once the process has been defined, the dermatologist must determine where the failure modes occur. Often, when assessing a particular multistep process, the team may determine that there are several steps with identified areas in need of improvement. One of the biggest mistakes made when first beginning to define a QI project is being too broad in the QI project objectives and trying to fix a large, complex process with a single project. Multiple small targeted QI interventions are more likely to be most successful at gradually fixing the whole process. Time and money are not limitless, so the next step in the quality improvement process is to focus the improvement effort and prioritize which step(s) to expend resources to improve. In many cases, a dermatologist can reflect and identify the specific step in the biopsy pathway where most errors occur in his or her office.

To help prioritize in the larger setting of a department or hospital, a full hazard analysis can be completed. The goal of a traditional HFMEA hazard analysis is to identify the most important components in a complex process on which to focus and improve. There are several sequential steps.^{12,13,21} First, the team lists all possible failure modes. Each potential failure mode is then assessed in terms of its severity (What is the impact on patient care if it occurs?), frequency (How frequently does it occur?), and detectability (How likely would the occurrence of this failure mode be obvious enough that it would be detected before an adverse event occurs?). A quantitative hazard score is generated by multiplying the severity, frequency, and detectability scores together. The failure mode with the highest

Table V. Interventions to reduce skin biopsy process errors

Process step	Intervention to reduce error
Decision to perform the biopsy is made	Stay up to date with medical literature or educational meetings regarding skin condition biopsy indications
Informed consent is obtained	Implement procedure checklist to include informed consent Log or confirm decision-maker name and number as standard hard stop in electronic medical record Use "teach back" technique Complete periodic simulation self-assessment to practice properly detailing informed consent
Biopsy details are determined	Review part I of this continuing medical education article Use decision support tools (VisualDX, UpToDate, textbooks, etc) Read-back label
Transport media/containers and requisition forms are obtained, labeled, and completed	Perform time out that includes procedure and transport media selection Confirm that label/requisition form details match Encourage open communication with dermatopathologists for quality assurance to develop systems-based solutions when problems arise
Surgical space, equipment, supplies, and staff are assembled, biopsy is performed	Review part I of this continuing medical education article Use decision support tools (VisualDX, UpToDate, textbooks, etc) Complete hands on technical training or periodic simulated self-assessment
Methods for documenting biopsy location(s) are performed	Mark biopsy site with skin marking pen Photograph biopsy site that includes regional information or body landmarks Location read-back to match documentation and photograph Double check photo/patient match when uploading photograph(s) to the electronic health record
Details of biopsy performance are documented	Document biopsy location while still in the room Implement procedure checklist that includes procedure note check
Communication/transportation pathway for biopsy specimen(s) and requisition form(s) from surgical space to dermatopathology laboratory is engaged	Perform time out to ensure label/requisition details match before transport and immediately upon arrival in dermatopathology laboratory
Dermatopathology laboratory performs diagnostic techniques using specimen(s) and a pathology report is generated	Use barcoded specimens Implement 1 specimen at a time throughput rather than batch Laboratory performs time out during processing to confirm label match
The pathology report is transmitted to the clinician who obtained the biopsy specimen	Automated process to release report to clinician upon sign-off by dermatopathologist Dermatopathology time out to confirm correct referring clinician Automated reminder systems for clinician result management Automated process to release report to clinician upon sign-off by dermatopathologist
The clinician determines a course of action/therapy for the patient based on the pathology report results	Structured time allotment for patient-related activities like results management Continuing medical education in clinicopathologic correlation and disease management
Results and proposed course of action/therapy are communicated	Electronic results disposal, including automatic prompt or identification of context patient or context primary care providers when disposing results Structured time allotment for patient-related activities like results management
Treatment of disease is initiated based on the pathology report results	Ensure the health literacy of communication to patients Practice "teach back" with patients Process to communicate delegated plans to staff

hazard score has the greatest potential impact on patient care.

Step 5: Define actions and outcome measures

In a full HFMEA analysis—again, typically performed in the larger setting of a department or hospital—once a cause within a subprocess is deemed worthy of pursuing, an appropriate course of action is proposed, a single individual responsible for implementing or overseeing that course of action is identified, and outcome measures to verify its progress or completion are selected. This might include additional equipment or resources to obtain, new clinical steps to enact, or old clinical steps to change or discontinue. This may also involve identifying the key stakeholders that currently are involved and the key stakeholders that need to be but are not yet involved. Once the change is implemented, all the changes should be described in the written office protocols to best sustain the improvement efforts. Table V shows possible actions to take to reduce errors in the various steps of the skin biopsy pathway.

Step 6: Remeasurement and reflection

Once the action and outcomes measures are determined, the project enters its intervention stage. The duration of time in the intervention stage will necessarily vary by project, but should be designed in as short intervals as possible to allow an adequate sample size of events for remeasurement. Typically, ≥ 2 remeasurements are performed after the intervention stage to determine initial and sustained progress with the changes sought for improvement. After each remeasurement and at the conclusion of the project, the dermatologist and team should purposefully reflect on the data and draw conclusions. Occasionally, an initial intervention plan is determined to be flawed, and modifications to the plan may be made during the intervention stage. Barriers to success should also be identified. It is important to note that failures to improve can be just as instructive as improvements. The process of trying to improve has recognized value. There is no stipulation by the American Board of Dermatology (ABD) that quantitative improvement must be realized to earn MOC credit for QI activity.

IMPROVING THE SKIN BIOPSY PATHWAY TO EARN MAINTENANCE OF CERTIFICATION COMPONENT 4 CREDIT

Key points

- **American Board of Dermatology diplomates can earn Maintenance of Certification credit**

by attempting to improve the skin biopsy pathway

- **A free, simple, focused set of online modules, designed for 1 person to complete in a relatively short period of time, has been created to assist the diplomate in assessing and improving the skin biopsy pathway in his or her office**
- **Assessment and an effort to improve the process fulfills the requirement**

For dermatologists who wish to assess potential practice gaps in their practice related to ≥ 1 of the steps in the skin biopsy pathway, this online module may be of value. In addition, it provides MOC credit as a practice improvement activity.^{22,23} To view and participate, visit <https://secure.dataharborsolutions.com/ABDermOrg/>.

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Answers to CME examination

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Skin biopsy

Biopsy issues in specific diseases

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Learning objectives

After completing this learning activity, the learner should be able to identify the appropriate site for biopsy for direct immunofluorescence; identify the appropriate site and technique for biopsy for alopecia and vasculitis; and identify the appropriate technique for biopsy for pigmented skin lesions.

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Editors

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Misdiagnosis may result from biopsy site selection, technique, or choice of transport media. Important potential sources of error include false-negative direct immunofluorescence results based on poor site selection, uninformative biopsy specimens based on both site selection and technique, and spurious interpretations of pigmented lesions and nonmelanoma skin cancer based on biopsy technique. Part I of this 2-part continuing medical education article addresses common pitfalls involving site selection and biopsy technique in the diagnosis of bullous diseases, vasculitis, panniculitis, connective tissue diseases, drug eruptions, graft-versus-host disease, staphylococcal scalded skin syndrome, hair disorders, and neoplastic disorders. Understanding these potential pitfalls can result in improved diagnostic yield and patient outcomes. (J Am Acad Dermatol 2016;74:1-16.)

Key words: basal cell carcinoma; bullous diseases; connective tissue diseases and porphyria; cutaneous T-cell lymphoma; dermatofibrosarcoma protuberans; hair disorders; malignant melanoma; neoplasms; panniculitis; primary cutaneous B-cell lymphoma; staphylococcal scalded skin syndrome; squamous cell carcinoma; Stevens–Johnson syndrome; toxic epidermal necrolysis; vasculitis.

INTRODUCTION

Obtaining a skin biopsy specimen is one of the most common and important procedures performed by dermatologists, and histologic examination of a biopsy specimen may represent the most informative and cost-effective test in all of medicine—yet little curriculum time is devoted to teaching this important

procedure. Many textbooks describe the surgical aspects of skin biopsy techniques, so that will not be the focus of this article. Rather, we will address important practice gaps that can affect patient outcomes, with a focus on potential pitfalls involved in performing skin biopsy examinations when specific disease entities are suspected. Clinical entities for

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which site selection and biopsy technique can have a profound influence on results include bullous diseases, vasculitis, panniculitis, systemic diseases, such as lupus erythematosus (LE), dermatomyositis (DM), drug reactions, Stevens–Johnson syndrome (SJS), toxic epidermal necrolysis (TEN), staphylococcal scalded skin syndrome (SSSS), hair disorders, and neoplastic disorders (**Table I**).

Important practice gaps include inappropriate site selection leading to false-negative direct immunofluorescence (DIF), decreased diagnostic yield of alopecia and vasculitis biopsy specimens, and inappropriate technique leading to limitations in the interpretation of pigmented lesions and patterns of nonmelanoma skin cancer.

BULLOUS DISEASES

Key points

- **The sensitivity of direct immunofluorescence is superior to that of indirect immunofluorescence or enzyme-linked immunosorbent assay for the diagnosis of pemphigoid**
- **Nonbullous lesional or perilesional skin from the trunk is preferred for the diagnosis of pemphigoid**
- **Brief immersion in formalin produces false-negative results in pemphigus but not in most other bullous diseases**
- **Saline is superior to liquid nitrogen, Michel medium, and Zeus medium for direct immunofluorescence specimens delivered to the laboratory within 48 hours**
- **Extracted anagen hairs may be adequate to demonstrate diagnostic direct immunofluorescence findings in patients with pemphigus**

Accurate diagnosis of autoimmune bullous disease depends upon clinicopathologic correlation and supportive studies showing circulating autoantibodies and their pattern of deposition in skin or mucosa. In the setting of bullous pemphigoid (BP), DIF has been shown to be more sensitive than indirect immunofluorescence (IIF) or enzyme-linked immunosorbent assay (ELISA).¹ Of the commonly used assays, DIF is the most sensitive (90.8%), followed by IIF (76%) and ELISA (ranging from 59% for BP230 to 73% for BP180). ELISA assays for BP180 can be falsely negative in 7.8% of BP patients, because the antigen maps to regions outside of the NC16A domain.² While the specificities of all 3 assays are close to 100%, false-positive DIF can be associated with bullous scabies, representing an important pitfall, especially in older individuals in nursing homes.

In addition, the choice of biopsy site can have an effect on the yield of the biopsy specimen. Biopsy specimens for DIF of immunobullous disease should be taken from nonbullous lesional skin or uninvolved perilesional skin within about 1 cm of a bulla (Fig 1).^{3,4} Both bullous skin and uninvolved skin farther from the bullae are associated with a higher rate of false-negative results. Lower extremity skin should be avoided when possible because of a greater risk of false-negative results.^{5,6} The specimen should be taken from above the waist if possible, and some experts advise trunk skin over extremity skin. It should be noted that most data regarding biopsy site choice are from patients with BP.

Specimens for light microscopy should show an intact vesicle or bulla if possible. If small vesicles are present, removal of an entire lesion is preferred. For larger lesions, the specimen should be obtained from the edge of a blister and should contain both portions of the blister and intact skin so that the edge of the blister and inflammatory infiltrate can be seen. A punch biopsy specimen works well for small vesicles and for perilesional skin because it allows for evaluation of the full thickness of the epidermis and dermis. A scooped shave biopsy specimen that extends into the reticular dermis may be useful to harvest larger bullae intact. Specimens for light microscopy should be placed in formalin for preservation. Tissue obtained for DIF should not be placed in formalin; rather, Michel or Zeus media can be used for preservation.^{7,8} Some immunodermatology laboratories accept specimens transported on normal saline-soaked gauze, and saline solution preservation has been associated with higher diagnostic yields. Standards for specimen acceptance vary, and the dermatologist should review the standards of the laboratory being used (**Table II**). Some require that fresh specimens be received during laboratory working hours—preferably within 6 hours of obtaining them—or specimens flash-frozen with liquid nitrogen and transported on dry ice. While some laboratories warn that specimens should not be immersed in saline solution, some data suggest that saline is actually a superior transport medium for DIF specimens. In a recent study of 25 specimens comparing 3 transport media, a diagnosis was reached in 92% after 24-hour saline exposure, 83% after 48 hours in saline, 68% after freezing in liquid nitrogen, and 62% after 48 hours in Michel medium.⁹ Specimens transported in saline feature decreased background fluorescence and enhanced specific fluorescence. The saline-split IIF technique can be performed on specimens transported in saline or Michel or Zeus media.

Table I. Suspected disease entities with recommended biopsy type, size, and requested laboratory tests

Disease	Recommended biopsy technique	Comments
Autoimmune bullous diseases	H&E—Saucerized removal of intact bulla if possible, or broad saucerization of periphery of bulla DIF—Perilesional skin ≤ 1 cm from bulla	Avoid lower extremity when possible because of delayed healing and greater risk of false-negative results
Epidermolysis bullosa	Saucerized removal of intact bulla if possible, or broad saucerization of periphery of bulla	Blisters >12 hrs old should be avoided; a fresh blister can be induced in clinically uninvolved skin, near a site where the patient usually blisters. Topical anesthetics should be avoided because they may induce artificial blistering
Vasculitis	H&E—Punch or deep shave of well-established purpuric lesion (>72 hrs old) DIF—Punch or deep shave of acute lesion (<24 hrs old)	IgA vasculitis is more likely to retain positive DIF findings in established lesions
Panniculitis	Deep incisional biopsy	Punch biopsy specimens tend to fracture, leaving inflamed or necrotic fat behind. An electric rotary power punch can overcome this limitation. A 6-mm punch is the smallest size that should be divided for culture and H&E. The edge of a necrotic focus provides a high yield for culture and special stains. The skin surface should be prepped with alcohol and allowed to evaporate. Deliver the culture specimen to the desk that handles fungal and AFB specimens
Lupus and dermatomyositis	H&E—Punch biopsy of an established lesion (>6 months old) that is still active DIF—Punch biopsy of lesional skin; choose an established lesion (>6 months old) that is still active	
SJS/TEN vs SSSS	Shave or punch biopsy including the full thickness of the epidermis	Desquamating sheets of skin may constitute an adequate specimen
Scarring alopecia	H&E— ≥ 4 -mm punch biopsy of an established lesion (>6 months old) that is still active DIF— ≥ 4 -mm punch biopsy of lesional skin; choose an established lesion (>6 months old) that is still active	For all forms of alopecia, avoid the active advancing border. Established lesions are preferred. One specimen can be bisected transversely 1 mm above the dermal/SQ junction, or it can be submitted intact for the laboratory to section transversely or with the HoVert or Tyler techniques. One specimen can be bisected vertically—half submitted in Michel medium for DIF and half added to the formalin bottle containing the transversely bisected or intact specimen
Nonscarring alopecia	For pattern alopecia or telogen effluvium— ≥ 4 -mm punch biopsy of an established area of alopecia For alopecia areata or syphilis— ≥ 4 -mm punch biopsy of an active lesion of recent onset is preferred.	If pattern alopecia or telogen effluvium is suspected, the specimen can be bisected transversely 1 mm above the dermal/SQ junction, or it can be submitted intact for the laboratory to section transversely or with the HoVert or Tyler techniques. For other forms of nonscarring alopecia, the specimen should be submitted intact
BCC/SCC	Shave or punch biopsy of adequate depth to show the invasive pattern and detect perineural invasion if present	In convex sites or thin facial skin, more superficial shave biopsy specimens may be appropriate. The skin should be pulled taught to provide greater control over depth. Avoid creating contour defects in sebaceous skin
Suspected melanoma	Complete excisional removal whenever possible	This may take the form of a saucerization
DFSP	Deep incisional biopsy	

Continued

Table I. Cont'd

Disease	Recommended biopsy technique	Comments
CTCL	Broad shave biopsy specimens below the depth of the DEJ are superior to punch biopsies	
Primary cutaneous B-cell lymphoma	Deep incisional biopsy whenever possible	A punch biopsy specimen or saucerization does not allow assessment of architecture

AFB, Acid-fast bacilli; *BCC*, basal cell carcinoma; *CTCL*, cutaneous T-cell lymphoma; *DEJ*, dermoepidermal junction; *DFSP*, dermatofibrosarcoma protuberans; *DIF*, direct immunofluorescence; *H&E*, hematoxylin–eosin; *IgA*, immunoglobulin A; *SCC*, squamous cell carcinoma; *SJS*, Stevens-Johnson syndrome; *SQ*, subcutaneous; *SSSS*, staphylococcal scalded skin syndrome; *TEN*, toxic epidermal necrolysis.



Fig 1. Biopsy specimens for direct immunofluorescence for suspected bullous pemphigoid should be taken from nonbullous lesional skin or uninvolved perilesional skin within 1 cm of a bulla.

In cases where the clinician or assistant has inadvertently placed a specimen for DIF into formalin, the specimen should immediately be removed and rinsed in normal saline. Evidence suggests that brief formalin immersion produces false-negative results for pemphigus, but not for diseases characterized by deposits at the dermoepidermal junction.¹⁰ Immunohistochemistry (IHC) for immunoreactants can be performed on formalin-fixed, paraffin-embedded tissue, but these immunostains are not widely available, and individual laboratories must validate the assays to determine the sensitivity and specificity relative to DIF. In the authors' experience, sensitivity decreases significantly when IHC methodology is substituted for DIF, and the assay should only be performed when a separate specimen for DIF cannot be obtained.

The root sheath of plucked anagen hairs may demonstrate positive immunofluorescence, especially in the setting of BP, and may prove adequate for diagnosis.¹¹ In this technique, an anagen hair is forcibly extracted from the scalp. The presence of a gelatinous follicular sheath above the hair bulb denotes an adequate specimen. For DIF biopsy specimens of mucosal surfaces, the tissue immediately adjacent to an erosion can be friable, and a tissue specimen from normal-appearing

mucosa 3 to 5 mm away may be preferable. For IIF studies, monkey esophagus is superior to human skin as a substrate, but the use of both substrates provides the maximum yield.¹²

For the diagnosis of inherited forms of epidermolysis bullosa (EB), immunofluorescent or immunohistochemical mapping can be used to localize the level of the split. In cases where mapping fails to demonstrate the level of cleavage, the diagnosis can be confirmed with transmission electron microscopy or mutational analysis. For electron microscopy, the specimen should be placed in a 2.5% glutaraldehyde solution (glutaraldehyde buffered by 0.1 M sodium cacodylate, pH 7.4) and stored at 4°C before overnight shipping at ambient temperature or with a cold pack if ambient temperatures are >37°C.

In most cases, mapping works quite well using antibodies to collagen IV and keratin 14. Specific monoclonal antibodies targeting EB-specific proteins are available in specialized laboratories. Information is available on the Dystrophic EB Research Association (Debra) International website (www.debra-international.org). The choice of biopsy location is key, because blisters >12 hours old may feature epidermal necrosis, proteolytic antigen degradation, or reepithelialization, resulting in a false assessment of the cleavage plane. A fresh blister can be induced in an area of skin that is clinically uninvolved, near a site where the patient usually blisters. The palms and soles should be avoided when possible because the increased skin thickness in these areas makes the induction of a blister and identification of the cleavage site more difficult. Topical anesthetics (eg, lidocaine 2.5% and prilocaine 2.5% under occlusion) should be avoided because they may induce artificial blistering, especially in the epidermis. Injectable anesthetics are preferred. Various methods have been used to produce the blister, including a cotton swab, pencil eraser, or gloved finger. Firm downward pressure is applied to the skin and traction is then exerted by twisting 180° in each direction until erythema is

Table II. Recommended handling and transport media

Test	Recommended transport media	Comments
H&E	Formalin	The specimen should ideally be fixed in ≥ 10 times the specimen's volume worth of formalin (overnight or first 24 hrs), then it can be placed in a smaller amount of formalin for shipping. Do not fill whirl pack bags more than half full for shipping. When shipping during the winter months, isopropyl alcohol should be added to the formalin in a 1:10 ratio to prevent freezing artefact
DIF	Normal saline, liquid nitrogen, Michel medium, or Zeus medium	Normal saline provides the highest yield if the laboratory accepts it, and it can be delivered within 24-48 hrs without freezing. Specimens transported in liquid nitrogen must not be allowed to thaw
Microorganism culture	Nonbacteriostatic saline	Deliver specimens promptly so they can be processed or refrigerated. Make arrangements with the laboratory and avoid shipping over weekends. If fungi are to be isolated, the tissue should be diced rather than ground. The fungal/AFB bench typically processes tissue in this fashion, while routine cultures are commonly ground with glass beads
Electron microscopy	2.5% glutaraldehyde solution	Store at 4°C before overnight shipping at ambient temperature or with a cold pack if ambient temperatures are $>37^\circ\text{C}$
Flow cytometry	Fresh specimen submitted on saline-soaked gauze or RPMI medium	

AFB, Acid-fast bacilli; DIF, direct immunofluorescence; H&E, hematoxylin–eosin; RPMI, Roswell Park Memorial Institute.

produced. For patients with mild skin fragility, ≤ 2 minutes of friction can be necessary to induce the blister. The biopsy specimen is obtained after a lag time of at least 5 minutes after the induction of erythema to allow the development of a microscopically identifiable blister. The biopsy specimen should include the border of erythematous and nonerythematous skin so that the split is clearly shown. As an alternative, children can be asked to perform an activity that typically induces a fresh blister just before the clinic appointment for obtaining a biopsy specimen. In patients with extreme fragility, the twisting motion of the punch biopsy itself may be sufficient to induce the cleavage plane necessary for diagnosis.

VASCULITIS

Key points

- **Biopsy specimens should show both the post-capillary venule and the deep plexus, especially for septic, rheumatoid, and antineutrophil cytoplasmic antibody–associated vasculitides, which are more prone to involve deeper vessels**
- **For the highest yield, biopsy specimens for hematoxylin–eosin staining should be taken from an established purpuric lesion (ie, >72 hrs old)**

- **For direct immunofluorescence biopsy specimens, an acute lesion (<24 hrs old) provides the highest yield**
- **Immunoglobulin A vasculitis often retains positive direct immunofluorescence findings in established lesions**
- **The biopsy yield for temporal arteritis increases with Doppler localization and harvesting of a 2-cm segment**

Biopsy specimens are helpful to distinguish vasculitis from nonvasculitic disorders and to distinguish between the different types of cutaneous vasculitis. In the setting of immunoglobulin A (IgA)-induced vasculitis, DIF studies are particularly helpful. Lesions <24 hours old are more likely to show immune reactants, and IgA is more likely to remain in vessels of established lesions compared to other immunoglobulins—although some data suggest that IgM may persist for up to 7 days in a significant number of specimens.¹³ The presence of IgA deposits correlates with a diagnosis of Henoch–Schönlein purpura with gastrointestinal, renal, and joint manifestations.¹⁴ Fibrin leakage is found in any vascular injury and is a prevalent but nonspecific finding. For light microscopy, biopsy specimens obtained from fully evolved lesions are more likely to have all of the diagnostic features of leukocytoclastic vasculitis. Biopsy specimens of

evolving lesions that are <24 hours old are likely to have some infiltration of neutrophils with karyorhexis, but often do not show expansion of the vessel wall or fibrin deposition. Septic vasculitis frequently features fibrin thrombi, endothelial necrosis, and the involvement of deeper arterioles. The latter 2 features are shared with rheumatoid and antineutrophil cytoplasmic antibody-associated vasculitis. Other forms of vasculitis are more likely to affect only the postcapillary venule with retention of an intact endothelial layer.¹⁵ After 48 hours, the inflammatory infiltrate in leukocytoclastic vasculitis begins to shift from a neutrophilic infiltrate to include lymphocytes and macrophages, but karyorrhectic debris and fibrin remain for extended periods.¹⁶

A well-developed purpuric lesion (ie, between 24 hrs and 1 week old) is usually adequate for hematoxylin–eosin-stained specimens, and we prefer a lesion that has been present for about 72 hours. The biopsy specimen should be obtained from the center of the lesion. In patients with livedo racemosa, a biopsy specimen should be obtained from the pale center of an erythematous ring. This is where the occluded vessel is most likely to be seen. When ulceration is present, the biopsy specimen should be taken from the trailing edge of the ulcer, rather than the ulcer itself, because any ulcer bed will demonstrate nonspecific vasculitis. If vasculitis involving a large muscular vessel is suspected, a deep incisional biopsy with step sections may be appropriate. Temporal artery biopsies should ideally be at least 2 cm, because specimens <0.7 cm may compromise the diagnosis.¹⁷ Doppler localization of the artery can be of help in planning the biopsy procedure.

PANNICULITIS

Key points

- A deep incisional biopsy provides the highest yield
- An electric rotary power punch or using the double punch technique are alternatives, especially in patients with a bleeding diathesis where a smaller biopsy specimen may be of benefit
- Gelfoam hemostasis is helpful for patients with a bleeding diathesis
- A 6-mm punch is the smallest size that should be divided for culture and hematoxylin–eosin staining
- The culture specimen should be diced rather than ground when attempting to isolate fungal and acid-fast bacillus organisms

Dermatologists are skilled surgeons and are well-suited to perform the deep incisional biopsies

typically needed for a definitive diagnosis of panniculitis.¹⁸ The surgery is generally well-tolerated, but potential risks must be taken into account, including scarring, infection, and poor wound healing. In situations where the history and physical examination lead to a high probability of a single diagnosis, the biopsy may not be in the patient's best interest. For example, classic erythema nodosum in a child with no other signs or symptoms is most likely related to previous streptococcal infection, and obtaining a biopsy specimen is not likely to change management. Lipodermatosclerosis is another diagnosis that can often be established with a fair degree of certainty without obtaining a biopsy specimen. When a biopsy is needed in this setting, the effect of stasis on delayed wound healing should be discussed with the patient as part of routine counseling before the procedure. In contrast, the histologic confirmation of erythema induratum, pancreatic panniculitis, infectious panniculitides, or subcutaneous panniculitis-like T-cell lymphoma can be critical to proper patient management. A deep incisional biopsy is typically needed, because punch biopsy specimens commonly fracture at the level of the inflamed fat, leaving the diagnostic portion of the specimen at the base of the wound. In select patients, including those with bleeding diatheses, a “power punch” (Fig 2) can overcome this obstacle and produce a diagnostic biopsy specimen with a small wound. Hemostasis can then be obtained with the use of Gelfoam (Pfizer, New York, NY) and gentle pressure. Electronic power punches were once commonly used to obtain hair transplant grafts, and many dermatology departments still have the equipment sitting in a storage closet. If the engine has worn out, the long metal punch can be attached to a variable speed Dremel tool placed in a plastic bag to comply with standard blood precautions. The rapid circular torque of the power punch typically produces a long intact cylinder of fat, even in patients with lobular necrosis. The major drawback of this technique is that the specimen is just 4 mm in diameter, and the pathologist may not be able to evaluate the full architecture and inflammatory pattern of the panniculus. In situations where it is difficult to obtain an intact specimen of necrotic fat, tissue culture and touch preparations for histologic examination may still lead to the correct diagnosis.¹⁹

CONNECTIVE TISSUE DISEASES AND PORPHYRIA

Key points

- Punch biopsy specimens should be ≥ 4 mm in diameter

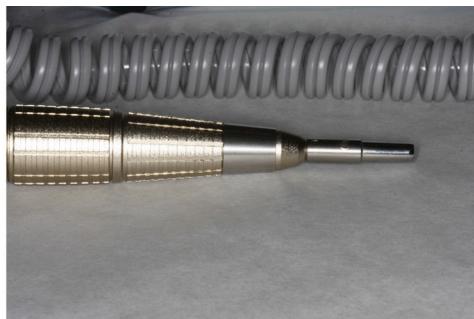


Fig 2. An electronic power punch is a good alternative for biopsy specimens obtained from patients with panniculitis, especially in patients with a bleeding diathesis. (Photograph courtesy Howard Pride, MD, Geisinger Medical Center.)

- In contrast to immunobullous disease, direct immunofluorescence of perilesional skin is of no value in most patients with connective tissue disease, because immune deposits are only present in lesional skin. One exception is the lupus band present in normal sun-protected skin in patients with active systemic lupus who are at risk of renal disease. This test has largely been replaced by assays for double-stranded DNA antibodies that identify the same population
- In the setting of chronic cutaneous lupus erythematosus, a punch biopsy specimen of an established lesion (>6 months old), but still active, provides the highest yield for both hematoxylin–eosin-stained sections and direct immunofluorescence
- Porphyria is commonly associated with hyalinization of superficial blood vessels which reveal strong immunofluorescence for immunoglobulin M and complement component 3

A diagnosis of chronic cutaneous lupus may require identification of compact hyperkeratosis, follicular plugging, interface dermatitis, basement membrane zone thickening, dermal mucin, columnar lymphoid infiltrate involving fibrous tracts, nodular lymphoid infiltrates involving the superficial and deep vascular plexus, infiltrates in the eccrine coil, or subcutaneous nodular lymphoplasmacytic aggregates with fibrinous lobular fat necrosis. In short, the key diagnostic changes may be present anywhere from the stratum corneum to the deep subcutaneous fat. An optimal diagnostic specimen to show these features should be ≥ 4 mm in diameter and can often be obtained using the punch biopsy technique extending to the subcutaneous fat; however, in the case of lupus panniculitis, a deep incisional biopsy may be required. Dermatomyositis often produces more superficial atrophic skin



Fig 3. Biopsy specimens for direct immunofluorescence for suspected chronic cutaneous lupus erythematosus should be taken from an established lesion (>6 months old).

lesions, and a shave biopsy may be adequate to show the diagnostic findings.

In contrast to immunobullous disease, DIF of perilesional skin is typically of little value in patients with connective tissue disease. Immune deposits are present in lesional skin in the setting of chronic cutaneous LE, and are best shown in an established lesion >6 months old (Fig 3). In the setting of systemic LE, the lupus band test on normal sun-protected skin has largely been replaced by assays for double-stranded DNA antibodies that identify the same population at risk for renal disease.

While some data suggest that positive immunofluorescence in sun-exposed skin is detected in only about one-third of patients with subacute cutaneous LE (SCLE), other groups have found a higher incidence (86% of patients). In contrast, while fluorescent dust-like particles are characteristic, some data suggest they are found in a small minority of patients with SCLE.²⁰ Positive DIF is noted in the majority of patients with established lesions of discoid or hypertrophic LE, and in lichenoid lesions of hypertrophic LE, DIF is the

single best test to differentiate the disorder from hypertrophic lichen planus.

The lilac inflammatory border of morphea reveals characteristic nodular lymphoplasmacytic aggregates involving both the superficial and deep vascular plexus. A deep punch or incisional biopsy specimen extending to the level of the subcutaneous fat is required to show these findings. More advanced lesions of morphea reveal a punch biopsy specimen with parallel sides resulting from dermal hyalinizing fibrosis with a loss of space between collagen bundles and the loss of periadnexal fat. This contrasts with the tapered appearance of most punch biopsy specimens. As with inflammatory morphea, a deep punch or incisional biopsy specimen is optimal to show these features. A diagnosis of superficial or atrophic morphea can sometimes be established with a more superficial punch or saucerized (scooped) shave biopsy specimen, especially if the loss of CD34 dendritic cells can be seen in the dermis.^{21,22} Even in superficial morphea, the biopsy specimen should include at least the upper half of the reticular dermis.

A diagnosis of porphyria cutanea tarda is suggested clinically by the presence of scarring, milia, and hypertrichosis in sun-exposed areas. Biopsy specimens of an intact bulla obtained using the saucerized shave technique typically have the diagnostic features of caterpillar bodies (ie, trapped remnants of the basement membrane zone sandwiched between layers of epidermis), a subepidermal split, festooning of dermal papillae, hyalinized superficial dermal vessels, and solar elastosis. Similar skin changes may be seen in variegate and coproporphyria. Erythropoietic protoporphyrina features more extensive hyalinization of vessels without solar elastosis. In all forms of porphyria with vessel hyalinization, DIF reveals strong vascular fluorescence with IgM, complement component 3, and often fibrin. Punch or scooped shave biopsy specimens that include at least the upper third of the dermis are adequate to show these findings. Transport media are chosen as for immunobullous disease.

STEVENS-JOHNSON SYNDROME, TOXIC EPIDERMAL NECROLYSIS, AND STAPHYLOCOCCAL SCALDED SKIN SYNDROME

Key points

- **The biopsy specimen must include the full thickness of the epidermis**
- **If the differential diagnosis includes fixed drug eruption, the biopsy specimen must also include both the superficial and deep vascular plexus**

also include both the superficial and deep vascular plexus

- **The roof of any old blister will become necrotic and mimic the full-thickness necrosis of erythema multiforme/toxic epidermal necrolysis; therefore, acute lesions are always preferred**

Stevens-Johnson syndrome (SJS) and toxic epidermal necrolysis (TEN) are associated with high morbidity and mortality, and an accurate diagnosis requires clinicopathologic correlation. The characteristic histologic features include satellite necrosis of keratinocytes that frequently progresses to full-thickness necrosis. Both conditions have an acute onset and progress rapidly, and the stratum corneum retains its normal basket weave architecture. A sparse perivascular lymphoid infiltrate is characteristically present, but features of fixed drug eruption (FDE), such as papillary dermal fibrosis, a polymorphous superficial and deep infiltrate with eosinophils, and perivascular melanophages are lacking. In patients with a clinical presentation characteristic for SJS or TEN, the roof of an acute blister or sloughed skin may be adequate for diagnosis, but when the differential diagnosis includes generalized FDE, the biopsy specimen must extend to the level of the subcutaneous fat so that both the superficial and deep vascular plexus can be assessed. Old bullae of any cause feature epidermal necrosis and can mimic SJS/TEN, so an acute lesion is preferable for biopsy whenever possible.

Staphylococcal scalded skin syndrome (SSSS) produces a split at the level of the stratum granulosum via acantholysis, which can be seen in biopsy specimens that extend to the level of the mid-epidermis. A sample of sloughed skin may be adequate to show the diagnostic features in many patients. The condition typically affects children because of their limited ability to eliminate the toxin. Adults with renal failure can also develop the disease, and in this population the major histologic differential diagnosis is pemphigus foliaceus. The 2 conditions can be identical in routine histologic sections but can be differentiated by DIF, IIF, or by a positive ELISA. It is likely that all media suitable for transportation of pemphigoid specimens would also be suitable for transport of pemphigus specimens. A major difference is that even brief immersion in formalin will completely extinguish pemphigus immunofluorescence, so a specimen inadvertently dipped into a formalin bottle must be discarded and a new specimen must be obtained.

When SSSS is suspected, appropriate cultures should be obtained from the suspected focus of infection. Intact bullae are sterile, but denuded areas of skin are prone to secondary bacterial colonization. Lesions of pemphigus foliaceus also become secondarily colonized within 1 to 2 days, so tissue culture of chronic skin lesions are of little value in the differential diagnosis.

HAIR DISORDERS

Key points

- More than 1 biopsy specimen may be needed to establish the diagnosis
- For all forms of alopecia, the active advancing border should be avoided because established lesions provide a higher diagnostic yield
- The punch should be ≥ 4 mm in diameter
- Place the punch at the same angle as the emerging hairs to avoid transecting hair follicles
- Hair density in different ethnic groups is now well established, so biopsy specimens of normal scalp for comparison are of limited value
- Transverse sections offer a higher diagnostic yield for pattern alopecia and telogen effluvium
- Serial vertical sections offer a higher diagnostic yield for most other forms of alopecia, including scarring alopecia
- Combining vertical and transverse sections provides the highest yield
- For lupus direct immunofluorescence specimens, choose an established but still active lesion (>6 months old)

To maximize the diagnostic yield of a scalp biopsy, a 4-mm punch biopsy specimen should be obtained from a well-developed lesion, preferably of several months' duration but still active (Fig 4). For DIF specimens in suspected LE, the lesion should be ≥ 6 months' duration. When biopsy specimens of active lesions are nondiagnostic, a biopsy specimen from a scarred area can be helpful diagnostically when evaluated with elastic tissue stains or polarized microscopy.²³⁻²⁶ Chronic cutaneous LE produces broad areas of scarring, whereas lichen planopilaris and folliculitis decalvans produce focal wedge-shaped scars at the level of the follicular infundibulum. Central elliptical alopecia of black women (the major form of central centrifugal cicatricial alopecia) is characterized by broad fibrous tract remnants with retention of the surrounding elastic sheath, contraction of the dermis, and thick



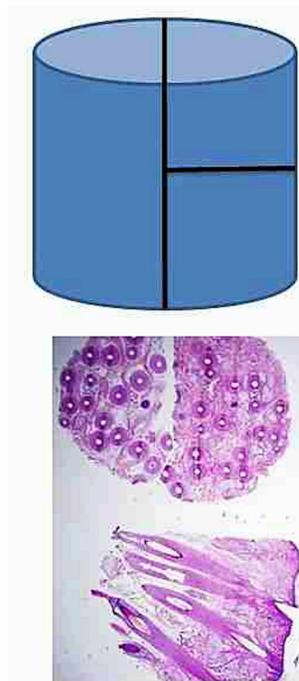
Fig 4. Biopsy specimens obtained from patients with scarring alopecia should be taken from well-developed lesions, preferably of several months' duration, but that are still active. Fully developed lesions provide a higher diagnostic yield when compared with the advancing border.

recoiled elastic fibers. Fluorescent microscopy of H&E-stained sections shows the pattern of elastic tissue without the need for a special stain, provided that excessive eosin is not used during the staining process. With polarized microscopy, fibrous tracts do not demonstrate birefringence in contrast to the birefringence of normal dermal collagen. A pattern of collagen birefringence sparing the fibrous tract remnants demonstrates good specificity for nonscarring alopecia, but the sensitivity is relatively low.²⁷

Both trichoscopy and confocal microscopy can be useful to increase the diagnostic yield through better site selection, directing the clinician to established areas of active inflammation.²⁸⁻³⁰ The punch should enter the scalp at the same angle as the emerging hairs to avoid transecting follicles. Hemostasis is easily obtained with Gelfoam, and the appearance of a punch biopsy scar that heals by secondary intention after Gelfoam hemostasis is generally superior to that after suturing of the biopsy site.

In the setting of scarring alopecia, diagnostic yield can be improved if 2 biopsy specimens are taken from developed lesions.^{31,32} One is bisected vertically, with one half placed in appropriate immunofluorescence media and the other half in formalin. The second specimen may be added to the same bottle intact or bisected transversely, 1 mm above the dermal/subcutaneous junction. A label should be placed on the bottle alerting the laboratory if the specimens are already bisected and that all 3 pieces should be embedded in a single cassette, cut side down. This technique provides the advantages of vertical and transverse sections at no added cost, because only one 88305 pathology Current Procedural Terminology code is reported for the 3 pieces of tissue in a single bottle.

Tyler Technique



HoVert Technique

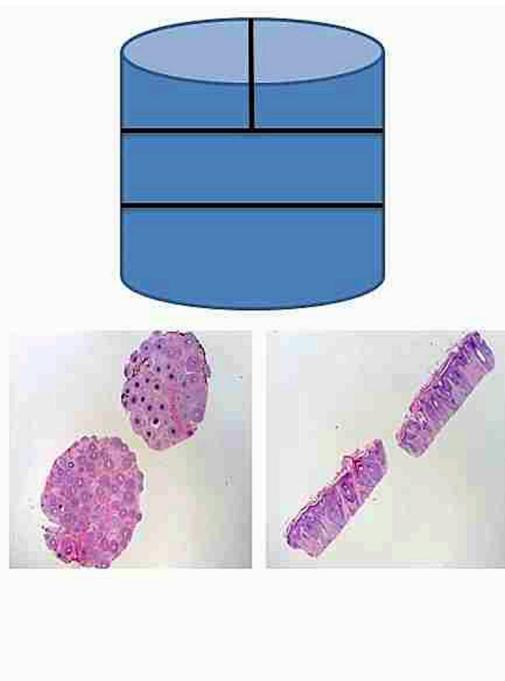


Fig 5. The Tyler technique involves vertical sectioning of the specimen, followed by transverse sectioning of one half. The 2 resulting half circles are embedded facing one another, fresh cut side down. The HoVert technique involves transverse sectioning of the specimen followed by vertical sectioning of the upper 1-mm portion.

Often, the laboratory only receives a single specimen. When the differential diagnosis is focused on pattern alopecia or telogen effluvium, transverse sections are superior and allow for accurate assessment of the proportion of anagen, catagen, and telogen follicles and the relative proportion of terminal and vellus hairs.^{33,34} For most other forms of alopecia, including all forms of scarring alopecia, vertical sections provide a higher yield than transverse sections alone.³⁵⁻³⁸ Serial sectioning of the specimen can increase the diagnostic yield.³⁹ Various techniques have been used to obtain the benefits of both vertical and transverse sections from a single specimen. The HoVert technique involves transverse sectioning of the specimen followed by vertical sectioning of the upper 1-mm portion. This allows better visualization of the follicular infundibulum—the site of involvement in lichen planopilaris.⁴⁰ The Tyler technique involves vertical sectioning of the specimen, followed by transverse sectioning of one half. The 2 resulting half circles are embedded facing one another, fresh cut side down. The technique results in the appearance of 1 vertical section next to 1 transverse section. In serial cuts, half of the transverse specimen demonstrates levels towards the subcutaneous fat, while the other half

demonstrates serial levels towards the epidermal surface (Fig 5).⁴¹ It should be noted that in conditions such as diffuse chronic telogen effluvium, >1 biopsy specimen at different points in time may be needed to establish the correct diagnosis.⁴²

NEOPLASMS

Key points

- **Shave biopsy specimens often fail to show an underlying invasive pattern or perineural invasion**
- **A broad shave biopsy frequently produces surrounding erythema and can create both an indistinct tumor border and the appearance of a growth that is larger than the original cancer**
- **Curettage specimens rarely allow for adequate assessment of tumor growth characteristics**
- **Punch biopsy specimens are more predictive of growth pattern but may not be suitable for all body sites**
- **If a shave biopsy specimen is obtained, the presence of spiky irregular tumor islands, fibroblast-rich stroma, or sclerotic red stroma suggest a more aggressive underlying growth pattern**

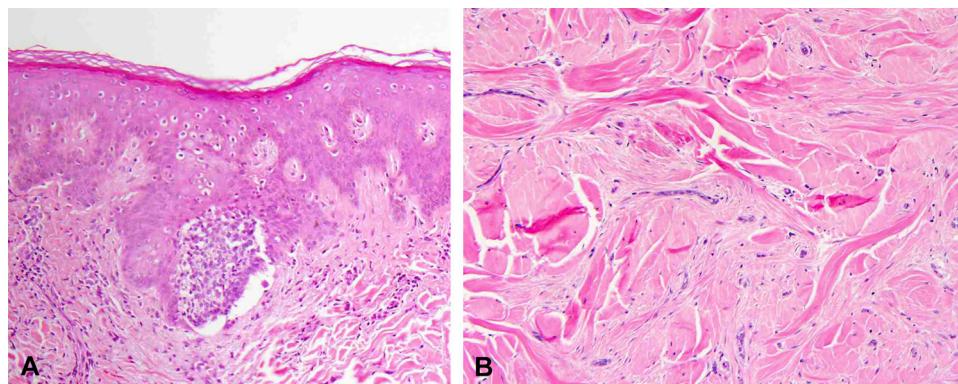


Fig 6. Superficial biopsy specimens of basal cell carcinoma may feature a superficial multifocal growth pattern (**A**) and may fail to show a deeper, more aggressive growth pattern (**B**).

Basal cell carcinoma/squamous cell carcinoma

A biopsy specimen is typically obtained before definitive treatment of suspected nonmelanoma skin cancer to confirm the diagnosis and because treatment decisions may be altered based on the growth pattern of the tumor. Visual examination, curettage, and dermoscopy have been used to define tumor extent before definitive surgery, but their accuracy is limited,⁴³ suggesting that scouting biopsies may be of use for poorly defined tumors that are not suitable for Mohs micrographic excision. Superficial and nodular basal cell carcinomas (BCCs) are best suited to defining tumor extent via curettage, whereas infiltrative, morphaform, and micronodular BCCs are surrounded by dense collagen, and the extent of the tumor cannot be defined by curettage of tumor and stroma.^{44,45} The same is true for desmoplastic squamous carcinoma and for tumors with perineural invasion, which may extend far beyond the clinically evident tumor margins.

The shave technique is commonly used in the setting of suspected BCC or squamous cell carcinoma, but a small (2-3 mm) punch biopsy specimen obtained from the center of the lesion may have advantages over a shave biopsy specimen.^{46,47} First, the tumor margins remain visible and distinct after performing a punch biopsy, whereas a broad shave biopsy frequently produces surrounding erythema that can create an indistinct tumor border or the appearance of a lesion that is larger than the original cancer. This could result in a larger than necessary excision to remove both the tumor and surrounding erythema. Punch biopsy specimens may also be superior to define the growth pattern of the tumor. Specifically, micronodular, morphaform, or infiltrative features may be present only in the deeper portions of a tumor (Fig 6).^{48,49} If observation and palpation suggest a superficial or nodular BCC or Bowen disease, shave biopsy may be

the preferred technique. The shave technique can be performed more quickly, costs less in supplies compared to alternative biopsy techniques, requires less instrumentation, does not require suture closure, and the resulting bleeding can be stopped with chemical cautery. In contrast, when a more aggressive growth pattern is suspected, a small centrally placed punch biopsy specimen can help to ensure the smallest definitive surgical excision of the tumor and the most appropriate therapeutic approach based on histologic subtype.

Either technique is superior to biopsy via curettage, which rarely allows accurate assessment of tumor growth characteristics. Regardless of the biopsy technique used, if spiky irregular tumor islands, fibroblast-rich stroma, or sclerotic red stroma are present, they suggest a more aggressive underlying growth pattern, and a deeper biopsy may be prudent before beginning definitive therapy.⁵⁰

Malignant melanoma

Key points

- Complete excisional removal is the method of choice for suspected melanoma whenever possible
- For macular lesions on the trunk, saucerization can achieve complete excisional biopsy and is often preferred by patients
- When the differential diagnosis is melanoma vs dysplastic nevus, a saucerization with a 0.5- to 2-mm margin of normal skin allows for assessment of the lesion and ensures a high likelihood of removal with clear margins
- The specimen can be scored, inked, or tagged at 12 o'clock to allow for orientation of the specimen
- Partial biopsy specimens are associated with a lower diagnostic yield, but there is no

evidence that tumor colonization of a deep punch biopsy wound worsens prognosis

- In the setting of lentigo maligna, a broad thin shave biopsy or multiple small shave biopsies offer a higher diagnostic yield than a punch biopsy
- An incisional biopsy is an excellent alternative when it can be oriented along a naturally occurring skin crease
- For multicolor lesions, each color in the lesion should be sampled
- Acral lesions should be bisected perpendicular to the dermatoglyphs (finger print lines) to avoid the artifactual appearance of confluence

Pigmented lesion biopsy may be the single most important intervention performed by dermatologists, because early detection is a key factor in determining prognosis in patients with melanoma. Complete excision is the method of choice for suspected melanoma when feasible because it allows the pathologist to judge symmetry and overall architecture.⁵¹ Partial biopsy specimens can lead to sampling error and an erroneous diagnosis, but may be performed in large lesions where complete excisional biopsy is impractical. The tumor may colonize deep punch biopsy wounds, but there is no evidence that such colonization is associated with a poorer prognosis. The greatest limitation of partial biopsy specimens is that they may compromise both diagnostic accuracy and staging.⁵² Evaluation of the remaining neoplasm after subsequent excision leads to tumor upstaging in roughly 21% of patients, with 10% subsequently qualifying as candidates for sentinel lymph node biopsy.⁵³ In a study of 157 cases of biopsy-proven melanoma in situ, subsequent excision revealed invasive disease in 8.3% of the lesions.⁵⁴

When feasible, excisional biopsy specimens should be oriented along the longitudinal axis on the extremities, because this reflects the pattern of lymphatic drainage and spread. Another option to minimize total tissue removed at the time of biopsy is to remove the lesion following the outline of the lesion itself with 1- to 3-mm margins. This can be performed in the manner of a Mohs micrographic surgery layer or via razor blade saucerization. For macular or clinically shallow lesions, the plane of saucerization is within the dermis, and primary closure is unnecessary. The sample provides the pathologist with the entire lesion, and the resulting shallow wound and round scar is often preferred by patients. The specimen can be scored, inked, or tagged at a designated site, such as 12 o'clock, to

allow for orientation of the specimen during gross examination and the subsequent histologic assessment of the lesion.⁵⁵ Full-thickness wounds may be closed primarily with temporary sutures without removing any additional tissue (ie, dog ears), because optimal cosmetic closure can be addressed after the definitive excisional surgery with margins.^{56,57} When closing the surgical defect of a suspected melanoma, undermining of the wound edges should be minimized, because this could theoretically affect sentinel lymph node mapping.

Lentigo maligna deserves special mention; the large size of the lesion often precludes complete excision. Misdiagnosis is common in small specimens because of the lack of effacement of rete ridges, areas of regression, and collision with nonmelanocytic pigmented lesions, such as benign lentigines and pigmented actinic keratoses.⁵⁸⁻⁶⁰ Punch biopsy specimens are associated with a high rate of false-negative results.⁶¹⁻⁶³ In the authors' experience, selection of the darkest portion of the lesion identifies the area with greatest pigment incontinence but is not necessarily the most diagnostic portion of the lesion. A broad thin shave biopsy specimen resembling properly cut prosciutto can provide the pathologist with a broad view of the junctional melanocytic proliferation without creating a deep wound. An excellent alternative may be multiple small shave biopsy specimens that sample every color and morphology within the lesion. These can all be placed in a single specimen bottle to maximize the chance of correct diagnosis and minimize cost, because only a single 88305 Current Procedural Terminology code will be billed. An elliptical incisional biopsy specimen is an excellent alternative when it can be oriented along a naturally occurring skin crease to hide the resulting scar.

Nevi on volar skin are often shallow and may be completely removed via saucerization. They are often characterized by elongated nests that follow the dermatoglyph furrows.⁶⁴⁻⁶⁷ Once removed, they should be bisected perpendicular to the dermatoglyphs to avoid the false appearance of junctional confluence. If you cannot trust your laboratory to do this, you should do it yourself and indicate that the specimen is already bisected.

Dermatofibrosarcoma protuberans

Key points

- A deep incisional biopsy specimen is required to show the growth pattern of dermatofibrosarcoma protuberans in subcutaneous tissue

- **Immunostains can be helpful in the diagnosis of indeterminate superficial biopsy specimens**

The pattern of infiltration into the subcutaneous tissue is a key diagnostic feature of dermatofibrosarcoma protuberans, and a deep incisional biopsy specimen is required to show this pattern. More superficial biopsy specimens can resemble cellular dermatofibroma, and immunostains or a second biopsy specimen may be required to establish a definitive diagnosis.^{68,69}

Cutaneous T-cell lymphoma

Key points

- **Broad shave biopsy specimens that include a wide area of the dermoepidermal junction are preferred to show the architecture of the infiltrate**
- **The epidermotropic population is the target for molecular studies, and broad biopsy specimens are also superior for immunostaining profiles and gene rearrangement studies**
- **Biopsy specimens from different anatomic sites that show an identical clone are helpful to establish the diagnosis in indeterminate cases**

Key diagnostic features of mycosis fungoides, the most common form of cutaneous T-cell lymphoma, include broad zones of papillary dermal fibrosis, vacuolar interface dermatitis with a lymphocyte in nearly every vacuole, and epidermal lymphocytes that are large, angulated, and hyperchromatic when compared to benign recruited dermal lymphocytes in the superficial dermis. A superficial perivascular infiltrate that spares the underside of the postcapillary venule is also characteristic. For the pathologist to see these diagnostic features, the biopsy specimen should extend to below the postcapillary venule (ie, to the upper reticular dermis). A gently saucerized broad shave specimen can be ideal, although punch specimens are often adequate. Because the malignant infiltrate is epidermotropic, more DNA for molecular studies can be extracted from broad shave specimens than from punch specimens. Shave specimens also provide a broader field of involvement for comparison of lymphoid populations in immunohistochemical studies. Plastic embedding of the biopsy specimen is sometimes employed, because it allows for 1- μ m thick sections that can show the cerebriform nuclear structure.⁷⁰

Clonality of the T cell population can be established by means of polymerase chain reaction (PCR)

or Southern blot analysis of T-cell receptor gene rearrangements (TCRs). While fresh tissue has a slightly higher yield, these studies can now be performed on formalin-fixed paraffin-embedded tissue. While most cases of mycosis fungoides express the alfa/beta receptor on the cell surface and stain with the BF-1 antibody, genomic rearrangements are commonly detected in the gamma chain genome because of the relative genetic simplicity of this portion of the genome. Testing for beta chain TCR can also be helpful, especially when the assay for the gamma chain demonstrates a germline configuration.

Any immune response is, by its nature, a clonal phenomenon, but the clones are quite small and the majority of T cells in a benign infiltrate are polyclonal T cells recruited by a small clone of memory T cells. In contrast, lymphomas feature expansion of a clonal population. Demonstration of an identical clone at multiple sites is highly suggestive of mycosis fungoides.⁷¹ When clonality in the skin matches that in the blood, mycosis fungoides is also highly likely. This is more likely to be seen in patients with advanced disease, but can also be detected in some patients with early disease.⁷²⁻⁷⁴

Immunophenotyping usually confirms T-cell origin ($CD3^+$) with strong predominance of $CD4$ over $CD8^+$ cells. Double negative or double positive $CD4/CD8$ phenotypes may occur, and the deletion of mature T cell antigens (such as >90% deletion of $CD7$ relative to $CD3$ in the epidermotropic compartment) is supportive of the diagnosis of MF.⁷⁵

Primary cutaneous B-cell lymphoma

Key points

- **Architecture of the infiltrate and zonal immunostaining patterns is critical to the diagnosis and is difficult to assess in small or superficial specimens**
- **A large incisional biopsy specimen is preferred**
- **If a smaller biopsy specimen is more appropriate for a given patient, a saucerization or deep punch specimen is superior to a standard shave biopsy specimen**

A skin biopsy providing an adequate specimen for histopathologic examination is key to the diagnosis of lymphoma. Incisional or punch biopsy specimens are generally preferred, but some sessile nodules can be removed effectively via saucerization, avoiding the crush artefact that sometimes accompanies punch biopsy specimens. If a punch is used, the biopsy should extend into the subcutaneous tissue, and a 6-mm punch is preferable when possible.

Small or superficial biopsy specimens impair adequate assessment of architecture and depth of involvement.⁷⁶

The specimen may be fixed in formalin because IHC, chromogenic in situ hybridization to establish kappa and lambda light chain restriction, and PCR-based gene rearrangement studies can be performed on formalin-fixed paraffin-embedded tissue.⁷⁷ If flow cytometry is to be performed, a fresh specimen submitted on saline-soaked gauze or Roswell Park Memorial Institute medium is preferred.

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Neurocutaneous disease

Cutaneous neuroanatomy and mechanisms of itch and pain

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Learning objectives

After participating in this learning activity, participants should be able to describe the nervous innervation of the skin, describe current knowledge of the mechanisms of pain and itch and their similarities and differences, and correlate innervations with possible mechanisms of action of drugs used in treatment of pain and itch.

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Few sources of information exist regarding cutaneous innervation and how to apply this basic neurologic science to the clinical treatment of itch, as often performed on a daily basis by dermatologists. We address the types of nerve fibers that innervate the skin and their different components and discuss the similarities and differences between itch and pain. We hope that increased knowledge of this topic will improve the recognition and treatment of neuropathic itch. (J Am Acad Dermatol 2016;74:197-212.)

Key words: cutaneous innervation; itch; nerve fibers; neuroanatomy; pain; pruritogens.

SKIN INNERVATION

The skin contains different types of nerve fiber endings, each with a different function. These nerve fibers are the axons from projecting neurons whose cell bodies are located in the dorsal root ganglia (DRG) or trigeminal ganglia (TG) and can be classified according to both diameter and myelination (Table 1). Large fibers ($A\beta$) are thickly myelinated and carry light touch and mechanical information. Small, thinly myelinated ($A\delta$) or unmyelinated (C) fibers are responsible for pain and temperature sensation. The nerve fibers that receive and transmit painful stimulus are called nociceptors; neurons that respond to pruritogenic

stimulus (pruriceptors) are a subset of nociceptors. $A\delta$ fibers constitute ~80% of the primary sensory nerve fibers; C fibers comprise ~20% of the primary afferents. Only about 5% of C fibers transmit itch.¹⁻³

Thinly myelinated or unmyelinated nerve fibers in the skin form what is called the “subepidermal neural plexus” or “subpapillary plexus” that consists of a mesh of nerve fibers that run parallel to the epidermis just below the tips of the dermal papillae. From this plexus, $A\delta$ and C fiber branches come out and enter the epidermis to course between keratinocytes as unmyelinated fibers. Nerves also divide to innervate sweat glands, erector pili muscles, hair follicles, and arterioles. Nerve bundles and single

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Table I. Classification of nerve fibers

Sensory nerves	Myelin	Diameter (μm)	CV (m/s)	Location/function
A α	Thick	12-22	70-120	Muscular spindles, tendon organs
A β	Moderate	6-12		Touch receptors
A δ	Thin	1-5	4-30	Polymodal, "first pain"
C	Unmyelinated	0.2-1.5	0.5-2	Polymodal, "second pain"

nerve fibers in the dermis are usually associated with capillaries. The papillary dermis also contains unmyelinated nerve fibers that form the dermal microvascular unit where axons often terminate in close proximity to mast cells. These are important in itch and allergic reactions. Thickly myelinated A β fibers are located in the reticular and papillary dermis.⁴⁻¹⁰

The skin also contains encapsulated nerve organs. Meissner corpuscles (MC) are cylindrical or pear-shaped tactile mechanoreceptors located high in the dermal papillae of the palms, soles, digits, nipples, and lips. MCs are innervated by intrapapillary myelinated endings (IMEs). One IME typically furnishes between 1 and 3 MCs per dermal papilla. Each MC contains a zigzag arrangement of unmyelinated terminal afferent nerve fibers.^{5,7,11-13} Pacinian corpuscles, in contrast, are ovoid pressure mechanoreceptors in the reticular dermis.¹⁴ The axons entering MCs and Pacinian corpuscles represent the specialized endings of A α and A β fibers.^{5,13} Studies in animals have also found unmyelinated axons.¹⁵

Mucocutaneous end organs are located in the papillary dermis of modified hairless skin at the mucocutaneous junctions (eg, the glans, prepuce, clitoris, labia minora, perianal region, and vermillion border of the lip). Two to 6 myelinated nerve fibers enter each mucocutaneous end organ and form many loops of nerve fibers resembling an irregularly round ball of yarn.⁴

Merkel cells are neuroendocrine cutaneous cells that are located in the basal layer of the epidermis and are concentrated in touch-sensitive areas of glabrous and hairy skin and in some mucosa. They are innervated by slowly adapting type 1 mechano-receptor nerve fibers, a subset of A β touch receptors, forming "touch domes." A Merkel cell-neurite complex or Merkel disk consists of the Merkel cell and the nerve fibers in close apposition to it. Other sensory fibers, including A δ and C fibers, also come into contact with Merkel cells.^{11,16,17}

ITCH

Itch can be classified by etiology. Pruriceptive itch originates from the activation of primary afferent

nerve terminals (eg, insect bites). Neuropathic itch is a chronic condition related to nerve injury that is sometimes associated with burning and stinging pain. Neurogenic itch is caused by central nervous system injury or activation without the activation of sensory nerve terminals (eg, renal disease and kidney failure). Psychogenic itch results from a pure central psychic processing disorder in the absence of skin pathology or underlying medical disease.^{18,19}

Itch mediators and receptors

Numerous itch mediators (pruritogens) and receptors (pruriceptors) have been identified (Table II), of which the best understood are histamine, proteases, opioids, substance P, the Mas-related G protein-coupled receptor (Mrgpr) family, and calcitonin gene-related peptide (CGRP).

Histamine. Histamine is the best known pruritogen. It is released from mast cells and keratinocytes and acts on neurons that express histamine receptors. H1 and H4 receptors are involved in itch signaling, whereas H3 receptor activation in mice is associated with a decrease in scratching behavior.²⁰ Once histamine binds to its receptor, it leads to the activation of transient receptor potential vanilloid 1 (TRPV1) ion channels.²¹ These are heat- and capsaicin-gated ion channels necessary for the histamine transmission of itch. Once TRPV1 channels are indirectly activated by histamine, the cell depolarizes, leading to the opening of sodium channels along the nerve and subsequent itch sensation. TRPV1 channels are expressed on primary afferent neurons, keratinocytes, dendritic cells, and mast cells. Their activation generates action potential and neuropeptide release. However, prolonged activation with resultant calcium influx can cause desensitization of the primary afferents and leaves the nociceptive and pruriceptive neurons inactive. Blocking or genetic silencing of TRPV1 receptors also reduces the scratch response induced by pruritogenic agents other than histamine, which suggests that TRPV1-positive neurons also express other itch receptors.²¹

The site of histamine release also changes the clinical manifestations of itch. The release of

histamine from mast cells in the papillary dermis leads to urticaria, with wheal and flare formation and itch. On the other hand, when histamine is released in the reticular dermis or subcutaneous tissue, it leads to angioedema, which is usually associated with pain more than itch.²²

Proteases. Proteases are another group of pruritogens that are released by leukocytes, keratinocytes, mast cells, endothelial cells, and platelets. Their itch effect is mediated by protease activated receptor-2 (PAR-2), which is expressed in small-diameter sensory neurons. Trypsine, tryptase, cathepsin S, and kallikrein-related peptidases (KLKs) are endogenous proteases. KLKs-5 and -14 activate PAR-2 and are upregulated in the lesional skin of patients with atopic dermatitis.²³⁻²⁵ Exogenous proteases can also activate PARs (eg, cowhage). The pruritogenic component of cowhage is mucucain, which stimulates PAR-2 and PAR-4 receptors. Proteases from dust mites and cockroaches have also been found to activate PAR-2.²⁶⁻²⁸ The activation of PAR-2 receptors may lead to nerve stimulation by gating the TRPV1 channel.²⁹ PAR-2 receptor activation also leads to the release of substance P and CGRP from peripheral and central nerve endings.

Opioids. Opioids are both pruritic and antipruritic. At the spinal level, μ -opioids are pruritic, whereas κ -opioids are antipruritic. Morphine-induced itch is histamine-independent and antihistamine resistant. It primarily occurs on the face, neck, and upper thorax, then often spreads rostrally from the injection site³⁰ and is inhibited by μ -opioid receptor (MOR) antagonists. Naloxone and naltrexone (MOR antagonists) have antipruritic properties, not only against morphine-induced itch but also against dialysis- and cholestasis-related itch that are usually resistant to antihistamine therapies.³¹⁻³³

Substance P. Substance P, when injected into human dermis, activates mast cells to secrete histamine.³⁴ It can also trigger the release of pruritogenic compounds from other cell types, such as keratinocytes, endothelial cells, and immune cells. Substance P acts on neurokinin-1 receptors (NK1Rs). Aprepitant (an NK1R antagonist) has controlled pruritus in case series of various dermatologic systemic disorders, Sézary syndrome, solid tumors, and erlotinib.^{35,36}

Mas-related G protein-coupled receptor family. The Mrgpr family includes MrgprA3 (a receptor for chloroquine), MrgprC11 (a receptor for mast-cell amide 2,6-dichlorobenzamide), and MrgprD (the receptor for B-alanine). MrgprA3- and MrgprC11-positive neurons need transient receptor

potential cation channel, subfamily A, member 1 (TRPA1) to elicit a scratch response in the same way that histamine-positive neurons need TRPV1 receptors. MrgprA3-positive fibers are C fibers.³⁷⁻³⁹

Calcitonin gene-related peptide. CGRP is the most abundant of all neuropeptides in human skin and is often found colocalized with substance P. In human skin, CGRP induces slowly developing local redness that can last for several hours. It has direct effects on blood vessels and does not induce histamine release.⁴⁰⁻⁴²

Itch pathways

Itch neurons (pruriceptors) are polymodal and respond to stimulus other than pruritogens, including heat and capsaicin. The selectivity theory of itch is the most largely accepted theory to explain why a stimulus is able to cause itch and not pain. Pruriceptors are a subset of nociceptors, and this theory postulates that itch occurs when these selective itch neurons are activated alone, while the sensation of pain dominates when itch and pain neurons are activated together. In this manner, inhibition of the itch pathway occurs via the nociceptive-only neurons.⁴³

The pathways that transmit itch stimulus to the central nervous system can be divided in 2 main groups: histamine-dependent and histamine-independent pathways. Histamine pruriceptors are unmyelinated, mechanoinsensitive C fibers afferent neurons. They have slower conduction velocities than other C fibers and have large innervation territories in the skin of the foot and lower leg (diameter of ≤ 85 mm).⁴⁴ Some of these fibers also respond to heat, which may explain why heat worsens many itch sensations and cooling improves it. Histamine also stimulates a small subset of mechanically insensitive A δ fibers.^{44,45} All other pathways that transmit itch and do not use histamine as a mediator are histamine-independent. For example, itch caused by cowhage spicules is mediated by mechanosensitive polymodal C and A δ fibers (as opposed to mechanoinsensitive C fibers for histamine pathways).^{46,47}

Once pruriceptors are activated, the impulse is transmitted to the spinal cord by different neurotransmitters. Histamine-evoked itch seems to be mediated primarily by glutamate, with gastrin-releasing peptide (GRP) playing some role.^{48,49} Histamine-independent itch is mediated by substance P, GRP, and glutamate.⁴⁹ In the spinal cord, GRP receptor-positive neurons located in the lamina I and the outer layer of the lamina II are thought to be relatively itch-specific. Mice with absent GRP receptors have normal pain perception

Table II. Itch and pain mediators

Mediator	Receptor	Expression, sources	Itch	Pain
Acetylcholine	Nicotinic (nAChR) and muscarinic (mAChR)	Cholinergic nerves, keratinocytes, lymphocytes, and fibroblasts	Itch in atopic dermatitis mAChR3	Produces pain
Capsaicin	TRPV1 receptor	TRPV1 afferent neurons, keratinocytes, dendritic cells, and mast cells	Effective in some chronic itch conditions	Initial burning sensation followed by desensitization
CGRP	CGRP receptor	Sensory nerve fibers and central terminals	Transmission of itch in spinal cord	Sensitization of primary afferents to heat
CRH and POMC	CRH-R1 and R2	Keratinocytes and mast cells	Releases histamine from mast cells	
Cytokines		IL-31 T cells and macrophages	IL-2; IL-31 increased in atopic dermatitis, pruritic in the skin	IL-1 β and TNF: increased IL-1 β facilitates release of CGRP from nociceptors; IL-10: decrease
Endocannabinoids	CBs (CB1, CB2)	Nerve, immune cells, keratinocytes, and hair follicles	Reduces itch peripherally; CB1 suppresses histamine-induced pruritus	Analgesic in the skin, spinal and supraspinal levels
ETs	ET-A and ET-B	Endothelium and mast cells	Direct pruritic (burning itch)	ET-A: algogenic; ET-B: analgesic
Histamine	H1 H4	Sensory nerve fibers	Typical pruritogen	Sensitizes nociceptors, recruits leukocytes, and enhances neuropathic pain in patients
Kallikrein and proteases	PARs	Leukocytes, keratinocytes, endothelial cells, mast cells, and platelets	PAR-2 increases itch, upregulated in itchy dermatoses	PAR-1: analgesic response to mechanical and thermal stimuli; PAR-2: hyperalgesia to thermal and mechanical stimuli, neurogenic inflammation
Kinins	Bradykinin receptors (B1R and B2R)	Endothelial cells and immunocytes	B2R antagonist reduces itch	Produces pain hypersensitivity by sensitizing peripheral nociceptor terminal and increasing glutamate transmission in the spinal cord
Leukotriene B4	Leukotriene receptors	Sensory nerve fibers and keratinocytes	Induces itch; mediates SP induction of itch	Produces hyperalgesia by activating neutrophil-mediator release
NKA and SP	Tachykinin receptors	Sensory nerve fibers	SP releases TNF α , histamine, LB4, and PGs from mast cells	Increase of mast cell TNF α and central sensitization
NGF, BDNF, and NT	TrkA (NGF), TrkB (NT-4, BDNF), and TrkC (NT-3)	Keratinocytes, mast cells, fibroblasts, and eosinophils	Involved in peripheral sensitization and inflammation	Involved in hyperalgesia and peripheral sensitization; upregulation of TRPV1; upregulation of substance P and CGRP
Opioids	μ , κ , and δ	Neurons and keratinocytes	μ Antagonist and κ agonist reduce itch; μ agonists are pruritic	Analgesic in the skin, spinal and supraspinal levels
PACAP and VIP	VPAC receptor	Autonomic and sensory nerve fibers, lymphocytes, dermal endothelial cells, and Merkel cells	Induce histamine release from mast cells	

PGs	Prostanoid receptors	Sensory nerve fibers and keratinocytes	PGE2 induces itch in humans (not mice); PG2 reduces immunoglobulin E-mediated scratching in mice	PGs induce hyperalgesia in the periphery and spinal cord
	P2X and P2Y	Sensory nerve fibers, Schwann cells, and immune cells		Adenosine applied peripherally elicits pain and hyperalgesia; spinal administration reduces tactile allodynia
	5HT receptors	Dorsal root ganglia	Induces itch when injected intradermally, enhanced by PGE2	Inhibition: spinal projection from raphe nucleus to lamina 1 and 2 of spinal cord; enhances pain: peripherally, released by platelets
	Purines and adenosine triphosphate Serotonin			

5HT, 5-Hydroxytryptamine; BDNF, brain-derived neurotrophic factor; CGRP, calcitonin gene-related peptide; CRH, corticotropin-releasing hormone; ET, endothelin; IL, interleukin; NGF, nerve growth factor; NKA, neuropeptide A; NT, neuropeptide; PACAP, pituitary adenylate cyclase-activating peptide; PAR, protease activated receptor; PG, protease activated receptor; POMC, proopiomelanocortin; SP, substance P; TRPV1, transient receptor potential vanilloid 1; VIP, vasoactive intestinal peptide; VPAC, VIP and PACAP receptor.

but reduced scratching behavior.⁴⁸ B-type natriuretic peptide (BNP) also plays a role in the transmission of itch in the spinal cord.⁵⁰

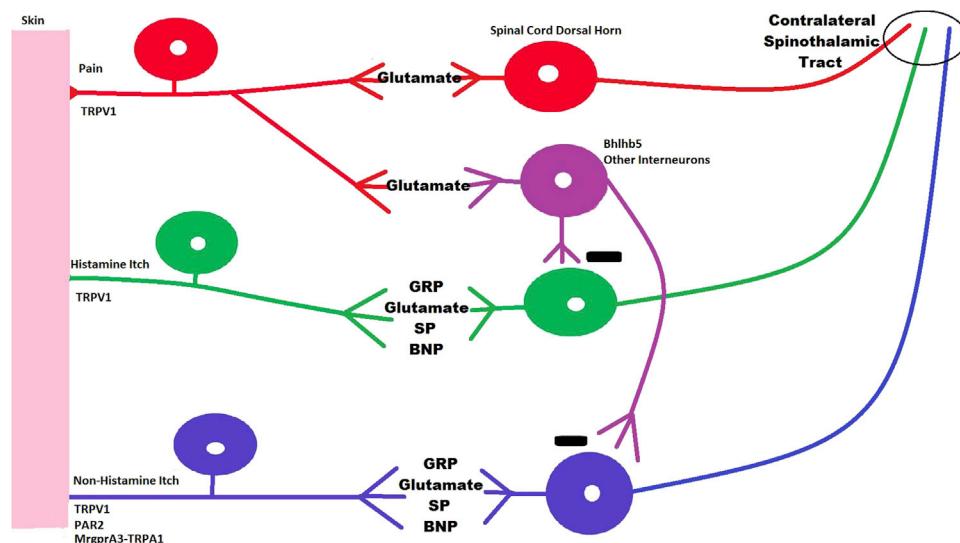
The cells bodies of itch neurons are located in the dorsal root ganglia of the spinal nerves and trigeminal ganglion. When the itch stimulus reaches the spinal cord, the impulse from pruriceptors is received by neurons located in the lamina I of the dorsal horn of the spinal cord. The projections of these neurons seem to maintain the histamine-dependent and -independent separation. These projection neurons do not feature spontaneous activity as the pain processing projection neurons do. This lack of spontaneous activity may be caused by active inhibition exerted by pain processing neurons.⁵¹ The itch spinal neuron projections cross to the contralateral side and ascend in the spinothalamic tract to the ventrocaudal part of the nucleus medialis dorsalis (MDvc), which then projects to the anterior cingulate and dorsal insular cortex. Positron emission tomography studies have found activation of the prefrontal cortex, premotor area, and anterior cingulate cortex in response to itch. Coactivation of the ipsilateral premotor areas might reflect the desire to scratch.⁵²⁻⁵⁴ In the spinothalamic tract, there is still a division of histamine- and nonhistamine-dependent itch pathways (ie, different neurons carry different stimuli).⁵⁵ Fig 1 is a simplified version of the itch pathway in the spinal cord.

PAIN

Pain mediators and receptors

Different pain mediators can generate painful sensations after they act on pain receptors or nociceptors (Table II). Nociceptors are located at the free nerve endings of unmyelinated C fibers and lightly myelinated A δ fibers. These nociceptors can be activated by noxious mechanical, thermal, and chemical stimuli. Mechanosensitive nociceptors are activated specifically by pressure and mechanical stress. Mechano-heat sensitive nociceptors also detect heat above a threshold of 43°C to 45°C. Most nociceptors are polymodal—they respond to different stimuli—and are linked to C fibers.⁵⁶

Electrophysiologically, A δ nociceptors can be divided in 2 main classes. Type I (high threshold mechanical [HTM] nociceptors) respond to both mechanical and chemical stimuli but have a relatively high heat threshold (>50°C). They will sensitize (ie, the heat and mechanical threshold will drop) in settings of tissue injury. Type II A δ nociceptors have a much lower heat threshold but a high mechanical threshold. Activity of this afferent

**Fig 1.** Itch and pain pathways in the spinal cord.

is thought to mediate the “first” acute pain response to noxious heat. Type I fibers likely mediate the first pain provoked by pinpricks and other intense mechanical stimuli.⁵⁷

Pain sensation originating from the surface of the skin consists of 2 different subtypes, first pain and second pain, and are perceived one after another with a time lag between them. First pain is “stabbing” in quality and is mediated by A δ fibers; second pain is “burning” in quality and is mediated by C fibers.⁵⁷

Different types of pain are related to the activation of different nerve fibers. Paresthesias and dysesthesias are caused by the spontaneous discharge of myelinated A β fibers. Lancinating and burning pain are caused by the spontaneous discharge of A δ and C fibers.

Some of the most important pain mediators and nociceptors include opioids, proteases, TRPV1, transient receptor potential cation channel subfamily M member 8 (TRPM8), sodium channels, and calcium channels. Opioids work at the spinal level, reducing nociceptor and increasing pruriceptor activity. Morphine has opposite effects on itch (pruritogenic) and pain (analgesic) that are mediated by distinct isoforms of the MOR.

The role of proteases in the pain pathway is similar to their role in itch generation (see above); proteases are also involved in neurogenic inflammation and thermal and mechanical hyperalgesia. They act mainly on PAR2 receptors.

TRPV1 is the receptor for capsaicin and is responsible for its response to heat stimulus. Other

receptors, such as TRPV2, 3, and 4, are also thought to be involved in heat sensation.^{57,58}

TRPM8 is a cold- and menthol-sensitive channel. Other cold-sensitive channels possibly include TRPA1, Nav 1.8, and K channels (TRAAK and TREK 1).^{59,60} Cold is known to relieve itch.⁶¹

The sodium channels Nav 1.7 and Nav 1.8 are important for pain transmission. Loss of function mutations in Nav 1.7 are responsible for severe deficits in pain perception.⁶² Gain of function mutations lead to Nav 1.7 hyperexcitability and 2 distinct pain disorders in humans: erythromelalgia and paroxysmal extreme pain disorder, both with intense burning sensations.^{63,64} Nav 1.8 is also responsible for heat and mechanical stimuli responses and is able to respond to cold. Serotonin and norepinephrine reuptake inhibitors, such as duloxetine, may reduce pain by blocking sodium channels.⁵⁷

Calcium channels also play a role in pain transmission. After neuronal damage, calcium channels are expressed at high levels. The expression of the $\alpha 2\delta$ subunit of voltage-gated calcium channels in C fibers of the DRG correlates with the development of injury-evoked hypersensitivity and allodynia. This subunit is the site of action of medications, such as gabapentin and pregabalin, which may explain their benefit in cases of chronic pain syndromes and fibromyalgia. N- and T-type calcium channels are also expressed in C fibers and are upregulated in models of diabetic neuropathy or other forms of nerve injury.⁶⁵ One N-type calcium channel blocker,

omega-conotoxin GVIA (ziconotide), has been used intrathecally to provide relief for intractable cancer pain.⁶⁶

Pain pathway

Painful stimuli are transmitted by nociceptors to the spinal cord, where they connect to spinal cord neurons. A δ nociceptors project to lamina I and to the deeper dorsal horn (lamina V). The low threshold, rapidly conducting A β afferents, which respond to light touch, project to the deep laminae (III, IV, and V). On the other hand, C nociceptors project more superficially to laminae I and II. Neurons in lamina V receive convergent nonnoxious and noxious input via direct A δ and A β inputs and indirect C fiber inputs. These neurons are called wide dynamic range (WDR) neurons because they respond to a broad range of stimulus intensities.^{57,67}

Glutamate is involved in the transmission of peripheral pain signals to the spinal cord. α -Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation of dorsal horn neurons mediates the basic response to acute painful stimuli. N-methyl-D-aspartate receptors are physiologically blocked by a magnesium ion. This block is likely removed by repetitive depolarization, resulting in an amplification and prolongation of the noxious input in the spinal cord (see central sensitization below).^{68,69}

From the spinal cord, impulses are transmitted to the brain through the spinothalamic and spinoreticulothalamic pathways. Central processing of pain, such as the spatial, temporal, and intensity aspects of pain, are processed in the primary (S1) and secondary (S2) somatosensory cortices; affective and motivational components are located in the anterior cingulate cortex (ACC) and insular cortex. The modulating systems have their origins at different levels in the nervous system, with the final descending pathway originating in the mesencephalic periaqueductal gray matter (PAG) and raphe nuclei systems exerting both facilitating and inhibitory effects upon dorsal horn neurons.⁷⁰⁻⁷²

ITCH AND PAIN: SIMILARITIES AND DIFFERENCES

Pain inhibits itch, and scratching reduces itch. Cutaneous field stimulation causing pain was able to reduce histamine-induced itch up to 10 cm from the stimulated side.⁷³ In the same way that itch can be reduced by painful stimuli, analgesia can reduce pain yet worsen itch.⁷⁴

The spinal administration of μ -opioids has been widely shown to induce segmental pruritus as a side

effect. Based on these results, μ -receptor antagonists have been used to treat cholestatic pruritus.³² On the other hand, κ -opioid antagonists enhance itch in animals.⁷⁵ Buthorphanol, which is both a κ -opioid agonist and a μ -opioid antagonist, has been effective in chronic intractable itch without affecting the analgesic response.^{76,77}

Scratching and other painful stimuli activate mechanically sensitive polymodal C and A δ fibers, which probably inhibit itch through a central mechanism. Various mechanisms have been proposed in this regard⁷⁸:

- Itch signal being masked by the activation of nociceptors
- Descending inhibition from the midbrain can block itch at spinal cord level⁷⁹
- Central terminals of pruriceptive DRG neurons could be modulated by retrograde signaling (eg, cannabinoid or nitric oxide signaling) from dorsal horn neurons activated by counter-stimuli
- Inhibitory interneurons in the spinal cord are activated by nociceptive input and inhibit itch signal; this potentially involves connections between afferent nociceptors that release glutamate and at the same time activate interneurons (Bhlhb5, Basic helix loop helix transcription factor b5,-positive) that inhibit itch afferent stimulus⁸⁰

Peripheral and central sensitization

The mechanisms behind peripheral and central sensitization are important in the development and maintenance of chronic pruritus and pain (Table III).

Peripheral sensitization. Peripheral sensitization has been mostly studied in nociceptors and is characterized by a decreased threshold for activation, increased responsiveness, and the presence of ongoing activity.⁸¹ These changes lead to alterations in the properties of peripheral nerves and can occur because of damage to nerve fibers. There are different mechanisms leading to peripheral sensitization.^{82,83}

Inflammatory factors that are released from activated nociceptors or nonneural cells that reside within or infiltrate into the injured area (ie, mast cells, basophils, platelets, macrophages, neutrophils, endothelial cells, keratinocytes, and fibroblasts) can enhance excitability of the nerve fiber and lead to pain or itch, resulting in peripheral sensitization. These factors are referred to as the “inflammatory soup,” and include different molecules, such as bradykinin, serotonin, prostaglandins, neurotrophins, and peptides.^{84,85}

Table III. Similarities between chronic itch and pain

	Chronic itch	Chronic pain
Peripheral sensitization	Peripheral sensitization of C and A δ nerve fibers	Peripheral sensitization of C and A δ nerve fibers
Central sensitization	Alloknesis and punctate hyperknesia	Allodynia and punctate hyperalgesia
Mediators	Inflammatory soup and neurotrophins	Inflammatory soup and neurotrophins
Central nervous system areas	Anterior cingulate cortex, premotor area; possible left hemisphere dominance	Anterior cingulate cortex, premotor area, and somatosensory cortex I and II

Neurotrophins such as nerve growth factor (NGF) lead to peripheral sensitization and are not only increased in injured, inflamed tissues with localized pain and hyperalgesia but also in the skin of patients with atopic dermatitis and prurigo nodularis. NGF acts directly on peptidergic C fiber nociceptors, which express tyrosine kinase receptor. NGF produces profound hypersensitivity to heat and mechanical stimuli by functional potentiation of TRPV1 receptors and also by increasing the expression or other pronociceptive proteins, such as substance P, TRPV1, and Nav 1.8 channel. Anti-NGF antibodies have been used with some success in the treatment of knee and hip osteoarthritis pain; however, these treatments were limited by side effects, including osteonecrosis.^{84,86,87}

Increased neurotrophin levels lead to an increase in nerve density in the skin of patients with chronic itch conditions (eg, atopic dermatitis), which may be partly responsible for itch sensitization.⁸⁸ In a mouse model of atopic dermatitis, inhibitor of tyrosine kinase receptor (NGF receptor) reduced scratch behavior.⁸⁹

In addition to neurotrophins, injury promotes the release of numerous cytokines (eg, interleukins-1 β and -6 and tumor necrosis factor-alfa [TNF α]) that potentiate the inflammatory response and increase the production of proalgesic agents, such as prostaglandins, NGF, and bradykinin.

Nerve injury also leads to ectopic hyperexcitability through the upregulation of tetrodotoxin-resistant sodium channels and voltage-gated sodium channels.^{90,91} TRPV1 channel is also upregulated and can become activated at normal body temperatures. Other ion channels, such as TRPA1, TRPM8, or purinergic receptor P2X, ligand-gated ion channel 3 may also be altered during nerve injury.⁹² The $\alpha 2\delta$ subunit of calcium channel is also markedly upregulated after nerve injury.⁹³

Nerve injury also leads to a phenotypic switch. For example, brain-derived neurotrophic factor and substance P are normally expressed only in C fibers,

but after peripheral nerve injury can begin to be expressed in A fibers. These fibers then can acquire the capacity to produce central changes, such as central sensitization.^{94,95}

When itch peripheral itch sensitization has occurred, the threshold to evoke itch by histamine injection or electrical stimulation decreases—for example, in patient with atopic dermatitis.⁹⁶

Central sensitization. Central sensitization refers to the process through which a state of hyperexcitability is established in the central nervous system, leading to enhanced processing of nociceptive (pain) messages.

When central sensitization for itch is present, signals from primary afferents for pain or itch cause more intense activation of postsynaptic spinal neurons, which explains hyperalgesia (or hyperknesia). In addition, this affects not only the signals from pain (or itch) nerves, but also signals from A β nerves, whose activation usually induces tactile sensation. As a result, even mechanical or tactile stimulus can activate postsynaptic spinal neurons for pain or itch, leading to allodynia (or alloknesis)—and as a result, with central sensitization the pathways for pain and itch are multiplied. In patients with pruritic diseases, such as atopic dermatitis, this sensitization results in itch being evoked by stimuli that normally induce pain and inhibit itch.^{97,98}

Central sensitization is responsible for allodynia and punctate hyperalgesia in cases of pain and “itchy skin” and hyperknesia in the case of pruritus.

Allodynia is a painful sensation that comes from a normally painless stimulus in the uninjured tissue surrounding a site of trauma. This is called touch- or brush-evoked hyperalgesia and is mediated by myelinated mechanoreceptor units, but requires ongoing firing of afferent C nociceptors.⁹⁹

Punctate hyperalgesia is defined as a slightly painful pinprick stimulation being perceived as more painful in the secondary zone around an area of inflammation. It does not require ongoing activity

of primary nociceptors for maintenance and is mediated by A δ fibers.¹⁰⁰

Allokinesis or “itchy skin” is touch- or brush-evoked pruritus around a pruritic area. This sensation requires ongoing activity of primary afferents and is most probably elicited by low threshold of mechanoreceptors (A β fibers).¹⁰¹ Hyperkinesis is an excessive itch in response to pruritogenic stimuli and is mediated by A δ fibers.⁹⁷

In patients with chronic pain, a pruritogenic stimulus such as histamine can actually cause pain; likewise in patients with chronic pruritus, noxious stimulus can cause itch. Both are evidence of spinal hypersensitivity to C fiber input in both conditions.^{97,102,103} The similarities in central sensitization in chronic pain and chronic itch explains the response to neuropathic pain medications in cases of neuropathic itch.¹⁰⁴

The 3 main mechanisms for central sensitization include alteration in glutamatergic neurotransmission/N-methyl-D-aspartate (NMDA) receptor-mediated hypersensitivity, loss of GABAergic and glycinergic controls in the dorsal horn neurons, and glial-neuronal interactions.⁵⁷

Alteration in glutamatergic neurotransmission/NMDA receptor-mediated hypersensitivity. The postsynaptic NMDA receptor (a glutamate receptor) is one of the receptors that is known to be involved in pain via induction of central sensitization at the spinal level. Binding of glutamate is usually not strong enough to activate NMDA receptor because of Mg $^{2+}$ blockade. However, continuous activation of peripheral nociceptive afferents under conditions such as inflammation and injury leads to depolarization in the postsynaptic cells of the spinal cord, which then removes the Mg $^{2+}$ blockade from NMDA receptors, enabling them to be activated by glutamate binding. This leads to Ca $^{2+}$ influx and intracellular signal transduction cascades, which results in the phosphorylation of ion channels and subsequently in the excitatory postsynaptic potential. This strengthens synaptic connections between nociceptors and dorsal horn neurons, which in turn will exacerbate responses to noxious stimuli (generate hyperalgesia).^{69,105}

Loss of GABAergic and glycinergic controls. The loss of GABAergic and glycinergic controls (disinhibition) in the dorsal horn neurons after nerve injury leads to depolarization and excitation of projection neurons.¹⁰⁶

Glial-neuronal interactions. Microglia and astrocytes accumulate in the spinal cord around the injured nerve fibers. It is thought that adenosine triphosphate released after nerve injury targets the

microglial P2X receptors activating it. The activated microglia release different signaling molecules, such as TNF α and interleukins-1 β and -6, which enhance neuronal central sensitization and nerve injury-induced persistent pain. Peripheral nerve injury activates glia not only in the spinal cord but also in the brainstem, where glia contribute to supraspinal facilitatory influences on the processing of pain messages in the spinal cord (descending facilitation).¹⁰⁷⁻¹⁰⁹

TREATMENT OF CHRONIC ITCH

Chronic itch is a condition that can be difficult to treat. Multiple medications have been tried with different results. Table IV lists medications and substances that have been found useful in patients with chronic itch or pain.

Capsaicin. Capsaicin acts locally by desensitizing peripheral nerve fibers by depletion of substance P. Topical capsaicin was found to be effective for notalgia paresthetica in a randomized trial. Preparations up to 0.1% can be used.^{110,111} A case series reported good results with a high-dose capsaicin 8% patch in patients with brachioradial pruritus.¹¹² Limiting factors are the transient nature of substance P depletion, and therefore the need for application 3 to 5 times per day, as well as a burning sensation that is intensified by using on nonintact skin.

Pramoxine. The topical anesthetic pramoxine 1% or 2.5% has been found to be helpful in case reports of neuropathic itch. In 1 randomized trial, pramoxine 1% cream was helpful for uremic pruritus.^{111,113}

Lidocaine. In case series, a mixture of lidocaine and prilocaine 2.5% cream was helpful for notalgia paresthetica.¹¹¹

Menthol. Topical menthol activates TRPM8 channels, which stimulates A δ fibers that transmit cold stimulus. Cold can reduce itch. Concentrations of 1% to 5% provide short-term relief from pruritus.¹¹⁴

Glucocorticoids. Glucocorticoids can have an indirect antipruritic effect based on their antiinflammatory action. They can be used in different chronic pruritic conditions.¹¹¹

Calcineurin inhibitors. Calcineurin inhibitors, including tacrolimus and pimecrolimus, have been used topically in patients with inflammatory skin conditions and resistant anogenital pruritus. They activate TRPV1 channels, which mediates an antipruritic effect. They can cause a burning sensation that disappears with repeated use, similar to capsaicin.^{115,116}

Doxepin. A tricyclic antidepressant that also blocks H₁-receptors, topical doxepin 5% cream was

Table IV. Select medications used in chronic itch or pain

Drug	Mechanism	Uses in itch	Uses in pain
Tricyclic antidepressants	Inhibit 5-HT and norepinephrine reuptake; block Na and Ca channels and NMDA receptors	Uremic, idiopathic, and lymphoma-associated pruritus	Neuropathic pain
Mirtazapine	Inhibition of 5-HT2 and 5-HT3 and histamine receptors	Pruritus malignant cholestasis, lymphoma, uremia	Neuropathic pain
Lidocaine	Blockade of voltage dependent Na channels	uremic pruritus	Neuropathic pain
Carbamazepine/oxcarbazepine	Blockade of voltage-dependent Na channels		Neuropathic pain, neuralgia
Lamotrigine	Blockade of voltage-dependent Na channels and inhibition of glutamate release		Neuropathic pain
Gabapentin/pregabalin	Blockade of $\alpha 2\delta$ subunit of voltage-gated Ca channels	Neuropathic itch	Postherpetic neuralgia
Tramadol	Opioid agonist, inhibition of 5-HT and norepinephrine reuptake		Neuropathic pain
Capsaicin	Substance P depleter	Effective in neuropathic itch and from hemodialysis, psoriasis, and aquagenic	
Anti-NGF	Anti-NGF	Antipruritic	Analgesic
Pizotigen	5-HT2 receptor antagonist	Antipruritic (polycythemia vera)	
Aprepitant	NK1 receptor antagonist	Antipruritic (chronic pruritus, Sézary syndrome)	

5HT, 5-Hydroxytryptamine; NGF, nerve growth factor; NK, neurokinin; NMDA, N-methyl-D-aspartate; VIP, vasoactive intestinal peptide.

found to be helpful for atopic eczema and contact dermatitis in a randomized trial^{117,118}; however, it can cause drowsiness because of transcutaneous absorption and has been reported to cause allergic contact dermatitis.

Gabapentin and pregabalin. Gabapentin and pregabalin block the $\alpha 2\delta$ subunit of the voltage gated calcium channel and are effective in the treatment of neuropathic, uremic, and postburn itch.¹¹⁹⁻¹²² Given the risk of somnolence, doses should be titrated upward, advancing slowly from nightly to 3 times daily every 3 days. In addition, the seizure threshold is lowered for gabapentin, and abrupt cessation can precipitate seizures in rare cases.

Antidepressants. *Serotonin reuptake inhibitors.* In case series, paroxetine, sertraline, fluoxetine, and fluvoxamine have been helpful for chronic itch and not limited to psychogenic itch.¹²³⁻¹²⁵ Sertraline was effective for cholestatic itch in a small, double blind trial.¹²⁶ Mirtazapine has been effective in different types of itch, including cancer-related itch, even in small doses without antidepressant properties.^{127,128} Mirtazapine also helps prevent morphine-induced pruritus.¹²⁹

Tricyclic antidepressants. Tricyclic antidepressants, such as amitriptyline, have also been used

for both neuropathic and psychogenic itch and for familial lichen amyloidosis.^{111,130} Amitriptyline can cause QT prolongation, so a pretreatment electrocardiogram is recommended in patients who are at high risk for cardiac disease. Doxepin, a tricyclic antidepressant with a strong anti- H_1 receptor effect, has been used in patients with uremic pruritus.¹³¹ Both can cause sedation, are best used at night, and should be titrated slowly to achieve the desired effect.

μ -Opioid antagonists. μ -Opioid antagonists, including naltrexone, nalmefeme, and naloxone, have been effective in different types of chronic pruritus. Their role in uremic pruritus is not clear.^{132,133} A small case series also showed the benefit of topical naltrexone 1% for some chronic pruritic conditions.¹³⁴ They are contraindicated in people with liver dysfunction.

κ -Opioid agonists. The κ -opioid agonist nalfurafine was effective in uremic itch in placebo-controlled trials.^{135,136} Butorphanol (a κ -agonist and μ -antagonist) has also been effective in case series of intractable itch with non-Hodgkin lymphoma, cholestasis, and opioid use.¹³⁷ Butorphanol has the advantage of not reversing the analgesic effects of opioid therapy; however, it can

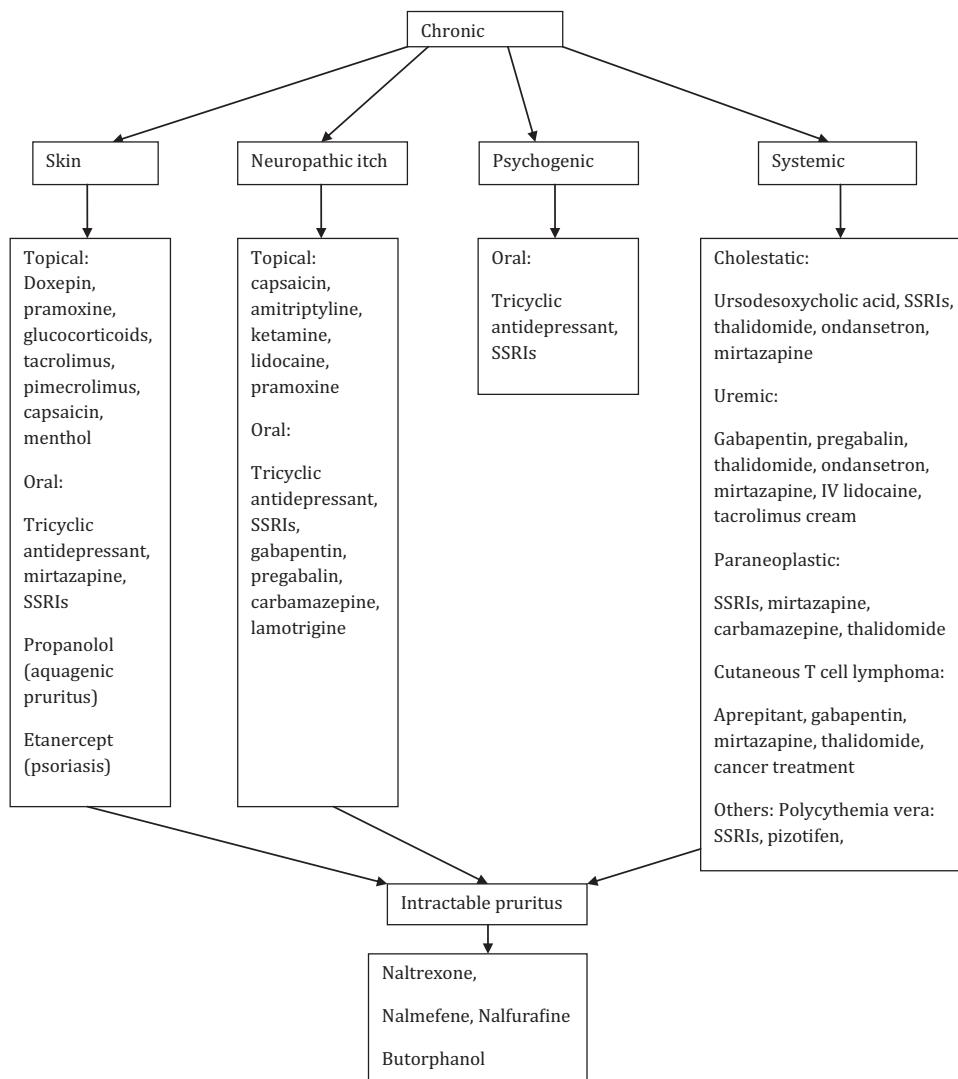


Fig 2. Algorithm for the treatment of chronic pruritus.

cause withdrawal in narcotic-dependent patients. Butorphanol can be used in patients with renal and liver impairment, but the dose should be reduced by 50%.

Ketamine. Topical ketamine 0.5% combined with amitriptyline 1% to 2% provided at least some relief in 60% of patients with different causes of localized neuropathic and genital pruritus in case series.^{138,139}

Propranolol. Propranolol was found to be effective for idiopathic aquagenic pruritus in a small case series. It is thought that blocking part of the sympathetic system may underlie its therapeutic effects.¹⁴⁰

Ondansetron. Ondansetron has helped patients with uremic pruritus and intractable pruritus in pediatric cases.^{141,142} However, placebo-controlled studies have not found benefit in cholestatic or

uremic itch.^{143,144} Ondansetron and other 5-hydroxytryptamine 3-receptor blockers have also been used to reduce pruritus induced by intrathecal morphine,¹⁴⁵ although at least 1 study did not find a benefit.¹⁴⁶

Thalidomide. Thalidomide can be effective in cases of refractory paraneoplastic pruritus. The mechanism of action is thought to be inhibition of TNF α .¹⁴⁷ It has also been found to help some cases of cholestatic-, uremic-, and mycosis fungoides-related pruritus.¹⁴⁸⁻¹⁵⁰

Lidocaine. Intravenous lidocaine given as a bolus has helped patients with cholestatic and uremic pruritus.^{151,152}

Antidopaminergic agents. Antidopaminergic agents, such as droperidol and alizapride, have been used to prevent intrathecal morphine-induced pruritus.^{153,154}

Carbamazepine. Carbamazepine, an antiepileptic sodium channel blocker, has been used for the treatment of neuropathic and paraneoplastic itch.¹⁵⁵ Lamotrigine, another antiepileptic with sodium channel blocking—properties, also helps patients with neuropathic pruritus.¹⁵⁶

Pizotifen. Pizotifen is a 5-hydroxytryptamine receptor antagonist that was effective in a small series of pruritus related to polycythemia vera.¹⁵⁷

Aprepitant. Aprepitant is a neurokinin 1 antagonist that is used to prevent nausea and vomiting associated with chemotherapy. It decreases mast cell activation¹⁵⁸ and has been shown to be effective for pruritus associated with cutaneous T-cell lymphoma and treatment with anti—epidermal growth factor receptor antibodies.^{159,160} In addition, a case report mentioned good effects in the treatment of brachioradial pruritus.¹⁶¹

Fig 2 shows a proposed simple algorithm for the treatment of chronic pruritus.

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Neurocutaneous disease

Neurocutaneous dysesthesias

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Learning objectives

After participating in this learning activity, participants should be able to properly detect patients with neurocutaneous disease, formulate a treatment regimen for cutaneous dysesthesias, and recognize patients who could benefit from referral to another specialist.

Disclosures

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Dysesthesia is a generic term for a cutaneous symptom—such as pruritus, burning, tingling, stinging, anesthesia, hypoesthesia, tickling, crawling, cold sensation, or even pain—with a primary cutaneous condition in a well-defined location that is often caused by nerve trauma, impingement, or irritation. There are multiple types of dysesthesias depending on the body location and the nerves involved. While location, exact symptoms, and etiologies might vary, the underlying theme is that these conditions are of neurologic origin and have dermatologic consequences. For many of these conditions, the symptoms are localized to the skin, and patients frequently present to the dermatologist; it is important for dermatologists to be knowledgeable about these symptoms and their underlying causes. In part II of this continuing medical education review, the primary diagnoses associated with underlying cutaneous dysesthesias will be explored, including scalp dysesthesia, trigeminal trophic syndrome, meralgia paresthetica, notalgia paresthetica, and brachioradial pruritus. The typical demographics in terms of symptoms, location, and patient populations will be discussed in addition to the specific etiologies, workups, and possible treatment options. (J Am Acad Dermatol 2016;74:215-28.)

Key words: brachioradial pruritus; burning scalp syndrome; dysesthesia; macular amyloidosis; meralgia paresthetica; neurocutaneous; notalgia paresthetica; scalp dysesthesia; trigeminal trophic syndrome.

A summary of neurocutaneous diseases is available in Table I.

SCALP DYSESTHESIA

Key point

- Thought to be caused by either psychiatric conditions or nerve trauma either indirectly

through muscle tension or directly through surgical trauma

Demographics

Scalp dysesthesia, also known as burning scalp syndrome, is indicated by burning, pruritic, or stinging sensations felt on the scalp of patients in the absence of a primary cutaneous disorder.^{1,2} These

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Abbreviations used:

ASIS:	anterior superior iliac spine
BRP:	brachioradial pruritus
LFCN:	lateral femoral cutaneous nerve
MP:	meralgia paresthetica
NP:	notalgia paresthetica
OMT:	osteopathic manipulative treatment
TENS:	transcutaneous electrical nerve stimulators
TTS:	trigeminal trophic syndrome

sensations can be either diffuse or localized.² Although previous case reports were comprised entirely of women,^{1,2} there has been no thorough epidemiologic evaluation, and the true sexual predilection is unknown. The incidence is also unclear, because most studies have used patient response questionnaires to look for “sensitive skin” localized to the scalp and therefore can not ensure that primary cutaneous diseases were not included.³⁻⁵

Etiology

Scalp dysesthesias have been seen in three patient populations; patients with a history of a psychiatric condition,¹ cervical spine disease,² and/or a history of a facial or brow lift.⁶ The psychiatric conditions described in association with scalp dysesthesias were dysthymic disorder, generalized anxiety, and somatization.¹ However, another retrospective review found no association between psychiatric disease, stress levels, and cutaneous symptoms.² Therefore, the relationship between psychiatric conditions and scalp dysesthesias is not well understood, as is whether there is causation or rather an unknown confounder. It is unclear if this association drives the primary disease or enhances patient propensity to be disturbed by these sensations.

The other two etiologic theories derive from neurologic trauma causing symptoms either more centrally with cervical spine disease or iatrogenically induced to peripheral nerves through surgical procedures. In the case of cervical disease, patients with scalp dysesthesias had a higher rate of C5-C6 radiographically localized cervical spine disease.² The nerves that originate from this C5-C6 location innervate the posterior neck and do not directly supply the scalp; the posterior scalp originates from C2.⁷ The hypothesis is that the nerve impingement does not cause a dermatome-related symptom, but rather that the symptoms are related to chronic tension placed on the occipitofrontalis muscle and scalp aponeurosis as a result of primary cervical spine disease.² When scalp dysesthesia is caused by a previous facial or brow lift, it is often because of surgical trauma to the superficial nerves of the face and scalp.⁶

Workup

Before making a diagnosis of scalp dysesthesia, the practitioner must ensure no primary cutaneous disorders are causing these symptoms, such as irritant contact dermatitis, seborrheic dermatitis, atopic dermatitis, or psoriasis.¹ If patients report a history of headaches or temporal pain caused by palpation, tension headaches or temporal arteritis need to be considered.¹ Once other diagnoses have been eliminated based on history or physical examination, the diagnosis of scalp dysesthesia can be entertained. As mentioned above, there are two main theories as to the etiology of the symptoms patients experience with scalp dysesthesia: psychologic and anatomic. Therefore, the two separate etiologic theories have two separate workup algorithms. While there might be a connection with underlying psychiatric conditions, there are not enough data to support psychiatric screening in these patients.¹ Because of the relationship with previous facial or brow lift surgical procedures, this is an important component of the history to ascertain. Because there has been a reported connection with cervical spine disease, one could argue for routine screening—however, this has only limited evidence.²

Treatment

Data regarding appropriate treatment strategies are lacking; many treatment options are based on case reports and have not been compared against each other, including oral gabapentin, topical gabapentin, topical corticosteroids (both high potency and low), antidepressants (eg, venlafaxine and amitriptyline),² doxepin,¹ and pregabalin.⁸ One case series with patients who had cervical spine-related symptoms had no improvement in their symptoms with physical therapy.²

TRIGEMINAL TROPHIC SYNDROME**Key points**

- Trigeminal trophic syndrome most commonly affects the V2 branch of the trigeminal nerve, resulting in ulceration of the nasal ala
- The most common cause of trigeminal trophic syndrome is trigeminal nerve ablation for trigeminal neuralgia and cerebral vascular accidents
- Treatment includes physical barriers, pharmacologic interventions, and surgical repairs

Demographics

Trigeminal trophic syndrome (TTS) is a condition in which abnormal sensations, as a result of trigeminal nerve injury, leads to self-inflicted ulceration of

Table I. A summary of neurocutaneous diseases

Disease	Symptoms	Etiology	Treatment
Scalp dysesthesia	Burning, pruritic, stinging sensations on the scalp without a primary cutaneous disorder	Unknown, but possible psychiatric condition, cervical spine disease (C5-6), or postsurgical changes	Gabapentin, topical corticosteroids, antidepressants (ie, venlafaxine or amitriptyline), doxepin, pregabalin, and physical therapy
Trigeminal trophic syndrome	Self-inflicted ulceration of the face, most commonly on the nasal ala	Damage to ≥ 1 branch of the trigeminal nerve, either direct injury or loss of blood supply	Physical barrier, gabapentin, carbamazepine, pregabalin, pimozide, and amitriptyline
Meralgia paresthetica	Paresthesia of the lateral or anterolateral upper thigh	Damage to the lateral femoral cutaneous nerve	Injection of lidocaine/steroids, capsaicin cream, lidocaine patches; physical therapy, chiropractic manual therapy, KinesioTaping, and acupuncture; surgical intervention
Notalgia paresthetica	Dysesthesia on the upper back between the vertebra and scapula (T2-T6)	Suspected alteration of the cutaneous sensory nerves of the upper back (localized impingement vs central damage/irritation related to spinal pathology)	Capsaicin, gabapentin, oxycarbazepine, and amitriptyline; transcutaneous electrical muscle stimulation, transcutaneous electrical nerve stimulators, osteopathic manipulative treatment, or physical therapy
Brachioradial pruritus	Pruritus, burning or tingling most commonly on the dorsolateral aspect of the arm, but also on the upper arm, shoulder/upper back, or upper aspect of the chest	Suspected either cervical spine disease (C5-6) or extensive solar damage	Topical therapies—capsaicin, doxepin, or amitriptyline/ketamine; oral therapies— gabapentin, lamotrigine, amitriptyline, valproate, and carbamazepine; surgical intervention; nonsteroidal antiinflammatory drugs

the face. The sensation associated with these ulcers has been described as itching, tickling, burning, or crawling, with most frequently an associated anesthesia;⁹ however, one case series reported that 50% of their patients had significant associated pain.¹⁰ If patients have complete or partial anesthesia, this is reported to cause a sensation of nasal blockage.⁹ Patients have also reported a sensation of drainage in the nasopharynx.¹¹ Regardless of the type of sensation, patients rub or pick at the area to relieve this sensation, resulting in ulceration.⁹ An important distinction to make is that these patients do not have any underlying psychologic or cognitive condition causing the picking—as in factitial dermatitis—but rather it is a manifestation of an abnormal cutaneous sensation.¹⁰

The nerve involved is the trigeminal nerve, which consists of three main branches: the ophthalmic (V1), the maxillary (V2), and the mandibular (V3). The ophthalmic branch (V1) supplies innervation to the forehead (supraorbital nerve), eyebrow/medial forehead/proximal nose (infraorbicular, supratrochlear, and lacrimal nerve), and the distal nose (anterior ethmoidal nerve). The maxillary nerve (V2) supplies innervation to the temple (zygomaticotemporal nerve) and the medial cheek/upper lip/nasal ala

(infraorbital nerve). The mandibular nerve (V3) supplies the preauricular cheek/parietal scalp (auriculotemporal nerve), cheek (buccal nerve), and the chin/lower lip (mental nerve).¹² The ulcers in TTS are usually unilateral and in the distribution of ≥ 1 branches of the trigeminal nerve.⁹ The prototypical ulceration is located on the nasal ala (Fig 1), involving the V2 branch of the trigeminal nerve; however, it can involve any of the three branches.¹³ Some specific case reports with unusual presentations include involvement of the scalp,¹⁴ oral cavity,¹⁵ tongue,¹⁶ full thickness eyelid defect,¹⁷ and even the lack of a corneal reflex,¹⁸ which then can lead to direct damage to the eye.¹⁹ The extent of ulceration can be significant, as seen in a case caused by herpes zoster, which led to ulceration through the forehead and frontal scalp into brain matter and resulted in frontal lobe damage.²⁰ The tip of the nose is often spared, which is innervated by the anterior ethmoidal branch of the nasociliary nerve, a distal branch of the ophthalmic nerve (V1).¹⁴ TTS has been shown to occur more frequently in women¹⁸; however, there appears to be no etiologic reason why women would be more at risk for this condition. It also has been reported more frequently on the right side of the face and in the V2 or maxillary division than the left side of the face.¹⁸



Fig 1. Trigeminal trophic syndrome. Extensive ulceration of the right nasal ala/sidewall in a patient who had a posterior inferior cerebellar artery occlusive cerebrovascular accident. Note complete sparing of the midline.

Etiology

TTs is a result of nerve damage to ≥ 1 branches of the trigeminal nerve either through direct injury or loss of blood supply. Wallenberg²¹ first described this disease in 1901 as a result of thrombosis of the posterior inferior cerebellar artery. The most commonly reported causes of TTS have been as a result of trigeminal nerve ablation for treatments of trigeminal neuralgia and cerebrovascular accidents, either thrombotic or from arterial dissection. When the cause is a thrombotic stroke, the most common location is in the posterior inferior cerebellar artery; when the cause is vascular dissection, the vertebral artery is most commonly involved.¹⁸ Other less common etiologies include craniofacial surgery, trauma, herpes zoster, herpes simplex, intracranial meningioma, other intracranial neoplasms, and leprosy.^{11,12,14,18,22-25} The time between damage to the trigeminal nerve and ulceration can vary from weeks to decades.^{18,24}

Workup

Trigeminal trophic syndrome is a diagnosis of exclusion with a large differential depending on the clinical circumstance. The differential includes: malignancy, Wegener granulomatosis, infectious etiologies, brown recluse bite, pyoderma gangrenosum, and factitious dermatitis.^{18,24} At this time, there is no specific algorithm to follow; however, patient history should include previous surgical history involving the face or skull and history of cerebrovascular accident, because these are the most common causative events. A skin biopsy specimen can be obtained to rule out many of the above listed

differentials. If no primary cutaneous cause is found for the ulcerations and the history supports the diagnosis with symptoms as mentioned above, TTS should be considered.

Treatment

TTS is a two-step disease: first, injury to the trigeminal nerve results in either anesthesia and/or paresthesia, and second, this change in sensation results in manipulation of the involved tissue and ulceration. Therapies target either or both of these steps, with goals to either repair the anesthesia/paresthesia with pharmaceuticals or surgical intervention or prevent ulceration through behavioral modifications.

The two primary approaches to treating the anesthesia/paresthesia have been through either medical or surgical intervention. Medical management has consisted of two modalities of treatment: physical barrier/behavior modification or medications that target the underlying neuropathy.

The many physical barrier methods attempt to prevent manipulation. Although techniques vary, the goal is that the barrier can be removed once the wound has healed and no further ulceration has developed; follow-up periods have ranged from months to years with no recurrences. This suggests that once the "habit" of picking is stopped, patients can prevent relapses. Physical modalities have been as simple as keeping nails short and wearing gloves at night²⁶ to using thermoplastic facemasks.^{19,27-29} The thermoplastic facemask most often attaches with straps that wrap around a patient's head.^{19,27,28} A similar physical barrier technique, with the added benefit of known wound healing benefits, was a case that showed improvement with a wound vac application.³⁰ However, in some locations, this application would be impractical. Instead of covering the ulceration, another case report showed benefit by limiting hand movements to the area of involvement with nighttime arm splinting.¹⁶

A physical technique that attempts to address the paresthesia component of the disease process is the application of a transcutaneous electrical nerve stimulation unit, which had mixed results because of associated pain.^{24,25}

Another medical option for treatment is pharmaceutical intervention. The different oral modalities include gabapentin, carbamazepine, pregabalin, pimozide, amitriptyline, and one study using alprazolam and citalopram synergistically.^{10,19,31-34} The most common medication used was gabapentin and the second was carbamazepine, both with varying results.¹⁸ One study saw improvement over

gabapentin alone when topical 0.1% tacrolimus ointment was used in addition to gabapentin.³⁵

In a case where the causative event was herpes simplex virus, treatment included acyclovir, occlusive dressings, and intralesional triamcinolone over 4 months. The only improvement of the ulcer was noted when triamcinolone was added—not with antiviral therapy or occlusive dressings alone. After a 20-month follow-up, there was no relapse. It is unclear if intralesional triamcinolone would be helpful in other etiologies of TTS, because in this case treatment was directed at the associated neuritis and possibly reducing nerve entrapment and irritation in the ulcer base.¹¹

Aside from medical interventions, there have been multiple attempts to correct the defect surgically. The most common reported graft technique is the paramedian forehead flap; however, other flaps have been used, including the forearm free flap²⁸ and the nasolabial flap,³⁶ with varying results. The paramedian forehead flap is most frequently used because the most common location for TTS is the nasal ala. In addition, when the corresponding trigeminal branch is not affected, innervated tissue is supplied via this method. It is thought that innervated tissue helps with the underlying dysesthesia^{37,38} and therefore prevents relapse. However, once division of the pedicle has occurred, the transplanted tissue becomes anesthetic; therefore, the flap might be of most benefit before the pedicle is detached to help break the “itch—scratch” cycle.³⁹

MERALGIA PARESTHETICA

Key points

- **Meralgia paresthetica affects the anterolateral thigh**
- **Meralgia paresthetica is caused by both iatrogenic and spontaneous causes, including weight gain, pregnancy, and constrictive clothing**

Demographics

Initially described by Bernhardt in 1878 and then independently by Bernhardt and Roth in 1895, meralgia paresthetica (MP) was previously known as Bernhard–Roth syndrome.^{40,41} It is also called lateral cutaneous nerve neuralgia.⁴² MP is the result of nerve entrapment/damage or other type of injury to the lateral femoral cutaneous nerve (LFCN). The LFCN is primarily a sensory nerve, but it also contains sympathetic fibers that control piloerection and vasomotor effects. It is comprised of several different combinations of nerves that originate from the L2-L3 lumbar nerves. The resulting paresthesia affects the



Fig 2. Meralgia paresthetica. The area of paresthesia (classically the anterolateral aspect of the thigh) is outlined.

lateral or anterolateral upper thigh (Fig 2) and has been described as burning, coldness, lightning pain, deep muscle achiness, tingling, frank anesthesia, or local hair loss.⁴³

MP has been classically described to improve with sitting and worsen with standing,⁴⁴ but other reviews have shown no positional relation.⁴⁵ It is traditionally accepted that MP is increased in patients who are obese, diabetic, and/or pregnant; however, information regarding the relationship of MP to weight status is conflicting, because some reviews show a correlation^{45,46} and others do not.⁴⁷ One study found that patients with MP are around two times more likely to have diabetes mellitus (DM) compared to age-, sex-, and body mass index-matched controls, and that the incidence of MP in patients with DM was 7.5 times that of the general population regardless of body mass index, age, or sex. MP symptoms usually develop before a patient's diagnosis of DM.⁴⁵

MP usually occurs in the adult population and, according to one population study, was seen equally in men and women and most often occurred between 40 and 60 years of age.⁴⁵ However, MP can also be seen in children.⁴⁷ MP appears to be more common than previously thought, with two independent population-based studies showing incidence rates around 3.26 or 4.3 per 10,000 person-years.^{45,47}

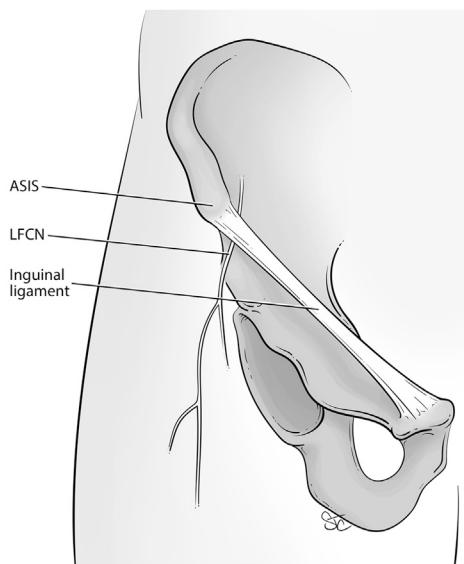


Fig 3. Anatomic position of the lateral femoral cutaneous nerve. The lateral femoral cutaneous nerve is particularly susceptible to injury because it passes 1 cm medial to the anterior superior iliac spine under the inguinal ligament.

Etiology

The anatomic location of the LFCN and its relationship to the anterior superior iliac spine (ASIS) is why this nerve is susceptible to injury. The most common path that the LFCN takes is 1 cm medial to the ASIS at the level of the inguinal ligament (Fig 3); however, there are many variations.^{44,48}

Numerous case reports include different causative events that can be grouped as spontaneous or iatrogenic. Some of the spontaneous causes include acute appendicitis,⁴⁹ ASIS avulsion fracture,⁵⁰ initial presentation of renal cell carcinoma,⁵¹ iliacus hematoma,⁵² simvastatin-induced,⁵³ poorly fitting clothing (including body armor⁵⁴ and low-cut pants^{55,56}), lipoma overlying the sartorius muscle,⁵⁷ spinal hydatid,⁵⁸ holster with accompanying pistol,⁵⁹ and radiographically degenerative pubic symphysis.⁶⁰ Reported iatrogenic causes, either by direct injury or by induction of scarring, include cesarean section or hysterectomy,⁶¹ femoral access for atrial fibrillation ablation,⁶² liver transplantation,⁶³ peritoneal dialysis,⁶⁴ laparoscopic inguinal hernia repair,^{65,66} spine surgery (particularly when using the Hall-Renton frame because of compression of the ASIS),⁶⁷ posterior lumbar spine surgery,⁶⁸ anterior approach total hip arthroplasty and hip resurfacing,⁶⁹ and bone graft harvesting.^{70,71}

Workup

The workup begins with history-taking and a complete physical examination. Important questions to ask are targeted toward musculoskeletal/

abdominal complaints, a history of surgical intervention, and clothing that compresses the hip/lateral thigh as seen above. In addition to a history of dysesthesia, pain, or anesthesia on the anterior/lateral thigh, there are some physical examination findings that can be helpful. Palpating the area can increase or elicit symptoms. There also can be tenderness over the lateral inguinal ligament where the LFCN can cross the ASIS and sometimes an associated area of hair loss, which is thought to be caused by frequent rubbing of the area because of the abnormal sensation.⁴⁴ Two maneuvers can help confirm the diagnosis: the pelvic compression test and the Tinel sign.⁷² The pelvic compression test is performed by having the patient lay on their asymptomatic side. The examiner then applies downward pressure on the pelvis for 45 seconds to see if symptoms improve. The improvement in symptoms is thought to be caused by relaxation of the inguinal ligament, reducing any tension on the LFCN.⁷² The sensitivity of this test is 95% and specificity is 93.3%.⁷³ The Tinel sign has been used in other settings to test for nerve irritation/sensitivity by eliciting symptoms by tapping the nerve in question. With MP, the LFCN should be percussed as it exits the inguinal ligament.^{72,74}

If the patient's history and physical examination are not enough to make the diagnosis, additional interventions and tests can be performed. The injection of bupivacaine 0.25% with epinephrine or lidocaine 1% around the LFCN where it passes near the ASIS or at the point of maximum pain can be performed for diagnostic purposes. If relief is obtained, this supports the LFCN as the source of discomfort.^{43,44,72} Further electrodiagnostic testing can be performed with two nerve conduction techniques: sensory nerve conduction velocity and somatosensory-evoked potentials.^{75,76}

The differential for MP includes lumbar root problems in L1-L3 or trochanteric bursitis.⁴³ To help distinguish between MP and spinal/lumbar root abnormalities, remember that lumbar disease follows a dermatomal distribution while MP does not. In addition, patients with MP should have a negative straight leg test and there should be no other neurologic, urogenital, or gastrointestinal symptoms. If there are, this should prompt referral and further workup.⁴⁰ Case reports have suggested that plain radiographic scans of the pelvis^{40,44} or computed tomographic scans of the lumbar spine should be performed to eliminate disc herniation, pelvic bony abnormalities, or pelvic tumors as potential causes of the symptoms. Ultrasonography or magnetic resonance imaging scans can also better evaluate the soft tissues of the retroperitoneum.⁴⁰

However, at this time, these additional tests are only recommended based on patient symptoms.

Because of the increased rate of DM in patients—and because this may be a preceding symptom—evaluation for DM has been suggested for this patient population.⁴⁵

Treatment

Conservative measures are initially used for symptom control, including nonsteroidal antiinflammatory drugs, protection of the area, avoiding compressive clothing, and weight loss.⁷² If discomfort/pain/abnormal sensations continue, an injection of lidocaine—using a similar method as described above for diagnostic purposes, with the addition of methylprednisolone—has shown to provide sustained benefit in most patients.⁴³ Two topical regimens that have shown benefit are capsaicin cream⁷⁷ and lidocaine patches.⁷⁸ However, with capsaicin, there was no sustained benefit after cessation of 5 times per day application.⁷⁷ The benefit of a lidocaine patch is less frequent application and given the location of symptoms, the patch would be discreetly hidden from view. One noncontrolled study in patients with DM found a benefit in treating associated pain by using botulinum toxin injections to the area of involvement.⁷⁹

Other alternatives include physical therapy, chiropractic manual therapy,⁸⁰ and KinesioTaping and acupuncture.⁷² Pulsed radiofrequency ablation has been reported to be helpful in patients with MP in case reports. This modality uses high-frequency alternating current, which ablates the nerve fibers without altering the surrounding tissues.⁸¹

The above interventions are most often the only treatment needed; however, for patients who still are suffering from symptoms, surgical interventions with either neurosurgery or orthopedic surgery can be discussed.

NOTALGIA PARESTHETICA

Key points

- Notalgia paresthetica symptoms are frequently located between the scapula and vertebral column
- Notalgia paresthetica is often associated with hyperpigmented patches/plaques
- Notalgia paresthetica can be associated with multiple endocrine neoplasia type 2A

Demographics

Notalgia paresthetica (NP) was first described in 1934 by Astwazaturow.⁸² Since that time, it has been called many things in the literature, including puzzling posterior pigmented purpuric patches, hereditary localized pruritus, puncta pruritica (itchy



Fig 4. Notalgia paresthetica. Hyperpigmented plaque extending to the medial edge of the scapula on the middle of the back. (Courtesy of Allison Legler, MD, Knoxville, TN.)

points),⁸³ localized shoulder pruritus,⁸⁴ and cutaneous lichen amyloidosis⁸⁵; however, the most widely accepted term is NP.

NP is described as pruritus, burning, a cold sensation, tingling, numbness, or even pain^{84,86} occurring on the upper aspect of the back between the vertebra and scapula between T2-T6.⁸⁷ Usually these sensations are only felt on one side of the back and not bilaterally.⁸⁴ The nerves that are responsible for sensation in this area are the medial cutaneous branches of the dorsal primary rami of the thoracic spinal nerves.⁸⁸ Upon inspection of the back, a hyperpigmented macule/patch⁸⁹ with occasional associated hyperkeratosis⁸⁴ (Fig 4) has been described to occur in the location of the dysesthesia. This hyperpigmented patch has sometimes been associated with amyloid deposition, which will be discussed further in the etiology section.

These patients typically do not have any known triggers or alleviating factors.⁸⁹ However one review found that patients with associated multiple endocrine neoplasia type 2A (MEN2A) show improvement with sun exposure.⁸⁵

The most common patient population affected by NP is women between the ages of 54 and 62 years of age⁸⁴; however it can be seen in any adult age group. There has been a documented association between MEN2A and NP. This uniquely occurs in younger patients, even children as young as 6 years of age.^{85,90,91} In patients with MEN2A and NP, the associated mutation has been reported to be RET mutations in codon 634.⁸⁵ Sometimes the development of NP can be an early sign of inheritance of MEN2A in affected families, but this does not seem to indicate a poorer prognosis.⁹¹

Etiology

The most widely accepted theory is that NP is caused by alteration of the cutaneous sensory nerves of the upper back. This was in fact one of the earliest

theories and was described in 1934 by Astwazaturow.⁸² However, there are several causes reported to result in this nerve irritation/trauma. Reports discuss both localized impingement caused by close association with surrounding muscle and also more central damage/irritation related to spinal pathology. The dorsal segments of T2-T6, which supply cutaneous innervation to the area between the scapular and vertebral columns, are prone to trauma or entrapment because of the right angle course they take while passing through spinal muscles.⁸⁷ One case series showed a relationship with injury to the long thoracic nerve and resulting dysfunction of the serratus anterior muscle with symptoms of NP. Dysfunction of the serratus anterior leads to retraction of the scapula, evenly subtly, which in turn places traction on the medial cutaneous branches of the dorsal primary rami causing symptoms of NP. These patients reported increased pain with or without pruritus with activities that required forward flexion of the arms (eg, driving or typing⁸⁸). This trigger might be limited to this unique subset of patients as this is not a commonly reported association with classic NP. However, the idea of tension on cutaneous branches of the thoracic nerves could be applied to other sources of scapula instability, such as trapezius injury, as a cause of NP.⁸⁸

Instead of muscle-induced tension/trauma to the nerves, the other theory behind the etiology of NP is that direct damage to the nerves because of spinal pathology results in symptoms. The causative spinal lesions have been reported to be osteoarthritic changes, kyphosis, vertebral hyperostosis,⁸⁴ and other degenerative changes^{89,92} corresponding to the T2-T6 dermatomes. Some suggest a connection with cervical spine disease instead of thoracic disease, given the previously described relationship between cervical disease and referred pain to the upper thoracic and infrascapular areas.⁸⁶ In a small study of 9 patients, electromyographic evaluation revealed denervation in the T2-T6 paraspinal muscles in the majority of patients with NP that corresponded to the localization of their symptoms,⁹³ further supporting a more centrally involved process; however, this could also support the muscular dysfunction theory.

An argument against central spinal pathology causing symptoms of NP is that the rate of abnormal magnetic resonance imaging scan findings of the spine in asymptomatic individuals can be as high as 73%⁹⁴; therefore, spinal processes might merely be an association. In addition, spinal pathology seen on plain radiographs in patients with NP has been shown to not always correspond with the affected dermatome.⁹⁵ In addition, if the nerve root is

affected, one would expect an entire dermatome to be symptomatic and not just one proximal section of the dermatome, as is seen in NP (ie, the area between the vertebrae and scapula).⁹⁵

Specifically in younger patients with NP, spinal pathology has not been found and therefore disease is suspected to be related to muscle entrapment⁹² as described above.

The etiology of NP in patients with MEN2A appears to be different than in other patient populations. The idea of an alternative etiology in MEN2A patients is supported by the fact that they present at an earlier age,^{85,90} when musculoskeletal changes are less likely in general. In addition, patients with MEN2A have no inherent increased risk of spinal or muscle pathology changes that would explain their associated risk of NP. In fact, one review found no association with spinal pathology and NP symptoms in patients with MEN2A.⁸⁵ The current theory is that NP in patients with MEN2A is related to the RET/glial cell line-derived neurotrophic factor signaling of neural crest cells that is also involved in embryologic development of the adrenal medulla and parafollicular C cells, which are involved in the other manifestations of MEN2A.⁸⁵

The etiology of the associated hyperpigmented patch/plaque as described above^{84,89} has been debated. This hyperpigmentation has been sometimes reported to show increased amounts of amyloid, which some believe is part of the primary process.⁸⁷ However, the most common theory is that the frequent rubbing or friction of this area leads to keratinocyte apoptosis and then amyloid deposition.^{84,96,97}

Another not as well supported theory is that symptoms of NP are caused by increased nerve fibers in the localized area of symptoms.^{97,98} However, this has not been a reproducible finding,⁹⁹ and it is unclear as to whether the increased nerve density is a result of or the cause of the pruritus and scratching.⁹⁷

Workup

Most frequently, the diagnosis of NP can be made by the reported history of pruritus, pain, and tingling in the location medial to the scapula, either unilaterally or bilaterally, in the setting of no other primary cutaneous findings. Upon examination, the practitioner can frequently find a hyperpigmented patch or plaque in the area corresponding to the patient's symptoms.^{84,89,90} Aside from the symptoms described above, there are usually no specific alleviating or triggering factors that help distinguish this diagnosis; however, one report described

worsening of symptoms with activities requiring forward flexion or extension of the patient's arms.⁸⁸

Given the association with thoracic and/or spinal pathology, one should obtain a history regarding previous neck trauma, motor vehicle accident, vertebral fracture, cervical neoplasm or malignancy, cervical disc disease, or a history of osteoarthritis.⁸⁶ However, unless specific symptoms suggest greater neurologic involvement—such as muscle weakness, spasticity, changes in reflexes, sensory changes other than localized to the periscapular region as described above, or other loss of function—routine spinal imaging or neurology referral is not recommended.^{89,100}

In pediatric patients with NP, one should consider checking calcitonin levels to screen for medullary thyroid carcinoma, because symptoms of NP can be an early manifestation of MEN2A.^{85,87,91} However, of note, in one case series the timing of development of symptoms of NP did not directly correlate with development of other disease states seen in MEN2A, such as pheochromocytoma or primary hyperparathyroidism.⁸⁵

Treatment

Multiple medical and physical modalities have been attempted, but there is no clear evidence as to which is superior because data are limited.

As in most other dysesthesias, capsaicin has been used in many case reports/series with mixed results specifically in the setting of NP. While it has been shown to be helpful in case reports, there is initial burning and discomfort with application and symptoms return with cessation of the medication.¹⁰¹⁻¹⁰³ Other topical treatments that have shown little benefit are corticosteroids and tacrolimus.^{84,104} Lidocaine 2.5% and prilocaine 2.5% (EMLA) cream used twice daily has been shown to be beneficial; however, symptom relief was not sustained with cessation of application,¹⁰⁵ similar to capsaicin. Systemic medications that have been tried with limited success include gabapentin,¹⁰⁶ oxycarbazepine,¹⁰⁷ and amitriptyline.¹⁰⁸ One of the few head to head trials comparing therapies was a nonrandomized, nonblinded study comparing topical capsaicin with oral gabapentin, which showed superior improvement with gabapentin. However, given the high risk of bias in this study, it is unclear if any significant conclusions can be made.¹⁰³

Because of its reported relationship with muscle instability, there have been several reported attempts to specifically target muscular dysfunction in hopes of relieving tension from the surrounding nerve fibers. In the case series where injury to the long thoracic nerve resulted in scapula instability, patients

received symptom relief with application of the transcutaneous electrical muscle stimulation (EMS) directly to the lateral scapula over the serratus anterior. This EMS unit alternated for 30 seconds on and off for a total of 15 minutes per day. The theory behind this therapy is that shortening overstretched muscle fibers counteracts the normally overstretched muscles holding up the scapula in the setting of denervation. This suggests that, other techniques that relieve traction of the stabilizing muscles of the scapula might help to improve symptoms.⁸⁸ Transcutaneous electrical nerve stimulators have also been shown to be beneficial when applied directly to the affected area.¹⁰⁹ Additional stabilization of the scapula by strengthening exercises for the rhomboids and latissimus dorsi has been shown to be beneficial in two patients.¹¹⁰ Improvement in symptoms with osteopathic manipulative treatment has also been shown to be beneficial in one patient; however, this patient was lost to follow-up 2 weeks posttreatment, so we do not know if this treatment had longstanding benefits.¹¹¹

Improvement in pruritus was seen in 5 patients treated with thrice weekly sessions of narrowband ultraviolet B light therapy for a range of 13 to 44 weeks; however, the mechanism of action is unclear in this setting.¹¹²

While an 18-month improvement of symptoms after local injection with botulinum toxin A has been reported,¹¹³ this result has not been reproducible in both a case series and a double-blind randomized control trial.^{113,114} The proposed theory of why botulinum toxin A would be beneficial is its in vitro effect on neurotransmitters involved in nociception,⁸³ such as substance P.¹¹³ Other interventions include paravertebral block of bupivacaine and methylprednisolone, which was shown to have resulted in resolution of symptoms at 12 months.¹¹⁵

BRACHIORADIAL PRURITUS

Key points

- Brachioradial pruritus is usually located on the dorsolateral aspect of the arm, around the elbow
- Brachioradial pruritus is often exacerbated by sun exposure

Demographics

Brachioradial pruritus (BRP) was initially named solar pruritus of the elbows/brachioradial summer pruritus and first described in 1968 by Waisman.¹¹⁶ BRP is a pruritic, burning,¹¹⁶ or tingling sensation¹¹⁷⁻¹¹⁹ that most commonly occurs on the dorsolateral aspect of the arm, around the elbow.^{117,120,121} Symptoms can, however, extend to the upper arm

and even include the shoulder/upper aspect of the back^{118,119} or the upper aspect of the chest.¹²⁰ BRP can occur on either one or both arms^{118,122} and is frequently bilateral.^{120,122,123} The locations of involvement are not always fixed and have been reported to spread to neighboring areas over time.¹¹⁹ There are usually no primary skin changes; however, secondary changes, such as excoriations, lichenification, or prurigo nodules from the underlying pruritus can be seen.^{116,119,123}

While the first reports of BRP described male patients,^{116,124} more recent reports seem to favor adult women.^{118,122} BRP can occur in all skin types,¹¹⁹ but it is most common in Fitzpatrick types I or II.¹²³ BRP is typically a sporadic finding; however, one case report described familial BRP, which occurred in 6 siblings and 5 of their children. In this family, there appeared to be either autosomal or X-linked dominant distribution.¹²⁵

The most common trigger for BRP is sun exposure, and therefore it often flares during the summer months.^{118,119,122,123} Some patients improve with cooler weather or preventing direct sun contact, such as with protective clothing.^{116,122} Patients frequently report improvement in symptoms with direct application of something cool. In fact the “ice-pack” sign is viewed as pathognomonic for BRP.¹²⁶ However, one case report mentioned cold temperatures as the cause for exacerbation.¹²⁷ In other cases, symptoms did not have seasonal variation.¹²⁸ In one report, the symptoms seemed to have seasonal variance only in locations where the intensity of the sun varied with the seasons and not in climates with more consistent high sun exposure.¹¹⁹ Early cases of BRP were reported in tropical or subtropical climates, but it has since been shown to occur in any geographic location.¹¹⁹

Etiology

There are two primary theories describing the etiology of BRP. One theory suggests that symptoms are related to cervical spinal disease; the other hypothesizes that symptoms are the result of extensive solar ultraviolet radiation exposure.

Multiple studies and case reports connect symptoms of BRP with cervical spine disease, particularly at the level of C5-C6.¹²² Although this is the most common location, cervical spine changes have been reported in multiple cervical levels, including C3-C7.^{122,123,127-129} These cervical spine changes are reported to consist of degenerative disc disease, intervertebral disc protrusion/bulging, spinal canal stenosis,¹²³ neuroforaminal stenosis, and space occupying lesions.¹²⁹ In addition to spontaneous changes to the spine, symptoms of BRP have occurred after

surgical interventions to the cervical spine, specifically cervical discectomy and fusion to C4-C6.¹¹⁸

The difficulty with associating cervical spine radiographic changes is ensuring that these findings are clinically relevant, because 75% of asymptomatic patients between 60 and 70 years of age have been shown to have degenerative disc disease changes.¹²⁵ In one retrospective review, the frequency of cervical spine changes was more frequent in patients with BRP compared to asymptomatic controls; however, there is the possibility for bias given that this study was performed at a tertiary referral center where patients may have had more severe disease.¹²⁰ In addition, in a large retrospective review of patients with BRP, further neurologic evaluation concluded that only 26% of the patients sent for evaluation had symptoms related to radiculopathy or peripheral neuropathy despite radiographic changes.¹²³ These expert opinions again question the exact causal relationship between the radiographic findings and the symptomatic disease.¹²³

The other main theory behind BRP is that symptoms are caused by extensive solar ultraviolet radiation exposure. Supporting the idea that BRP is not just solely caused by cervical disease is that the symptoms are frequently bilateral and associated with increased sun exposure as mentioned above,¹²² which is not classically seen in other nerve impingement scenarios. One study that possibly explains the seasonal variation and relationship to sun exposure found that during times of active symptoms, patients with BRP had decreased epidermal and dermal nerve fibers histologically when compared to times with no disease activity.¹³⁰ The decrease in nerve fibers is similar to what is seen in skin after serial phototherapy sessions.¹³⁰ However one might hypothesize that this decrease in nerve fibers would improve symptoms as phototherapy usually improves pruritus; the significance of this finding therefore has yet to be determined.

It is also possible that a combination of both cervical disease and sun exposure causes symptoms in patients with BRP.¹¹⁸ Potentially, chronic sun exposure and the resulting photodamaged nociceptors could fire spontaneously, which then could be amplified by nerves compressed by cervical spine disease¹³⁰—both “triggers” might be needed. One study found patients with seasonal variation of their symptoms were less likely to have cervical radiographic findings than patients without seasonal variation, so it is possible that these two groups of patients (ie, those with and without seasonal variation) have two separate etiologies of their common symptom.¹²² Clearly, more research is needed in this area to help further delineate these hypotheses.

Workup

The key to making the diagnosis of BRP is obtaining a thorough history with regard to potential triggers, such as sun exposure and an improvement of symptoms with the application of cool substance(s), and then exclusion of any primary cutaneous disorder occurring in the area of symptoms.^{118,127} Although there is a potential connection between BRP symptoms and cervical spine disease, radiographic findings are not always related to symptoms; given an unknown false positive rate,¹¹⁸ radiography is not recommended as part of routine workup. Signs that additional workup is needed, however, are symptoms that continue to worsen, a lack of response to conventional treatments, and additional evidence of muscle weakness or other neurologic dysfunction.^{118,123,128} Neck pain alone has not been correlated with abnormal radiographic findings.¹¹⁹ For additional workup, a referral to the neurology department is warranted for further imaging. Because of the superior ability of a magnetic resonance imaging scan to determine nerve impingement and soft tissue evaluation, this is considered the diagnostic tool of choice over cervical radiographs.^{119,123,125,131}

If evidence of spinal disease is found, one could consider referral to the orthopedics or neurosurgery departments to ensure that no surgical intervention is needed.¹²⁸ One additional benefit for radiographic confirmation of cervical spine disease is that this could potentially help target your therapeutic interventions.¹²⁸

Treatment

While determining the etiology of a patient's symptoms and whether they have cervical nerve impingement might help you determine where your therapeutic ladder should start, at this time the cost/risk benefit of routinely imaging BRP patients is unknown. Low-risk (topical) interventions should be attempted before systemic or surgical interventions or additional workup (unless the symptoms warrant more intervention).

Symptoms of BRP frequently are reported to worsen with sun exposure; an easy intervention is regular sun protection in the form of protective clothing.¹²¹ While some case reports show a benefit with the use of capsaicin cream,^{120,123} a small double-blind test comparing capsaicin and placebo found no significant difference.¹¹⁹ A frequent combination used is topical corticosteroids in conjunction with oral antihistamines, which has had mixed results—however, they are not usually beneficial.^{118,123,128} Topical doxepin has shown some benefit, but the most successful topical treatment has been with amitriptyline 1%/ketamine 0.5% cream

used 2 or 3 times daily with reports of complete resolution of symptoms.^{123,127} The amitriptyline blocks voltage-gated sodium channels, preventing depolarization of the axons, and ketamine blocks the synaptic transmission of nerve impulses. In four clinical trials, no significant systemic absorption of either amitriptyline or ketamine was found.¹²⁷

When topical treatments fail, systemic treatments are often used. The most common reported medication used is gabapentin, in doses varying from 300 mg daily to 300 mg 6 times daily.^{117,121,123,128,132,133} Other systemics tried with limited to no benefit have been lamotrigine,¹¹⁷ amitriptyline, valproate, carbamazepine,^{117,123} and nonsteroidal antiinflammatory drugs.¹²⁸

When symptoms are known to be caused by cervical spine disease, surgical intervention is an option and can be beneficial in relieving nerve compression and therefore symptoms.^{127,134} However, given the associated risks, it is usually not considered first-line therapy, is infrequently used in this setting,^{123,127} and should only be used once conservative measures have been taken. Less invasive options that have shown benefit include cervical steroid injections.^{120,129} Cervical spine manipulation has also been shown to be beneficial in a case series of 19 patients¹³⁵; however, in another case report, this was unsuccessful—it is unclear if similar mechanisms were used.¹³²

As has been reported in many other conditions, sometimes simply knowing the source of a patient's symptoms can be of therapeutic benefit for the patient.¹²⁰

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The spectrum of nephrocutaneous diseases and associations

Genetic causes of nephrocutaneous disease

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Learning objectives

After completing this learning activity, participants should be able to recognize the important relationship between the skin and the kidney inclusive of genetic syndromes, recognize and differentiate the cutaneous manifestations of multiple kidney-related disorders, and vice versa, and describe the pathophysiology and genetic basis of how renal disorders may potentially manifest on the skin, and vice versa.

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There are a significant number of diseases and treatment considerations of considerable importance relating to the skin and renal systems. This emphasizes the need for dermatologists in practice or in clinical training to be aware of these associations. Part I of this 2-part continuing medical education article reviews the genetic syndromes with both renal and cutaneous involvement that are most important for the dermatologist to be able to identify, manage, and appropriately refer to nephrology colleagues. Part II reviews the inflammatory syndromes with relevant renal manifestations and therapeutic agents commonly used by dermatologists that have drug-induced effects on or require close consideration of renal function. In addition, we will likewise review therapeutic agents commonly used by nephrologists that have drug-induced effects on the skin that dermatologists are likely to encounter in clinical practice. In both parts of this continuing medical education article, we discuss diagnosis, management, and appropriate referral to our nephrology colleagues in the context of each nephrocutaneous association. There are a significant number of dermatoses associated with renal abnormalities and disease, emphasizing the need for dermatologists to be keenly aware of their presence in order to avoid overlooking important skin conditions with potentially devastating renal complications. This review discusses important nephrocutaneous disease associations with recommendations for the appropriate urgency of referral to nephrology colleagues for diagnosis, surveillance, and early management of potential renal sequelae. (J Am Acad Dermatol 2016;74:231-44.)

Key words: autoimmune; dermatology; genetic; genodermatoses; inflammatory; nephrocutaneous; nephrology.

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Table I. Renal findings in nephrocutaneous genodermatoses and recommendations on the timeliness of referral to a nephrologist if a patient has suspected or actual signs/symptoms of renal disease

Genodermatosis	Renal manifestations	Referral timeline
Neurofibromatosis type 1	Renal artery stenosis, Wilms tumor, and angiomyolipoma	Urgent
Tuberous sclerosis	Angiomyolipoma, renal cysts, and renal cell carcinoma	Urgent
Beckwith-Wiedemann syndrome	Wilms tumor, nephrolithiasis, renal cysts, hydronephrosis, and calyceal diverticula	As clinically indicated
von Hippel-Lindau syndrome	Renal cell carcinoma (clear cell variant) and renal cysts	Urgent
Birt-Hogg-Dubé syndrome	Renal cell carcinoma (oncocytoma and chromophobe variants) and renal cysts	As clinically indicated
Cowden syndrome	Renal cell carcinoma (papillary variant)	As clinically indicated
Hereditary leiomyomatosis and renal cell cancer	Renal cell carcinoma (papillary, tubulopapillary, and collecting duct variants)	Urgent
Fabry disease	Progressive renal failure	As clinically indicated
Nail-patella syndrome	Glomerulonephritis and end-stage renal disease	As clinically indicated
Turner syndrome	Horseshoe kidney, urinary collecting system anomalies, and decreased renal blood flow	As clinically indicated

INTRODUCTION

There are currently no comprehensive, up to date publications in the dermatologic literature relating to the wide spectrum of associations between cutaneous dermatoses and renal pathology. This 2-part review discusses important nephrocutaneous disease associations with specific recommendations for the diagnosis, management, and appropriate referral to nephrology specialists.

Part I of this two-part review focuses on the genetic relationships of nephrocutaneous diseases, and part II addresses inflammatory and medication-related nephrocutaneous associations.

GENETIC CAUSES OF NEPHROCUTANEOUS DISEASE

Table I is a summary of renal findings in the nephrocutaneous-associated genodermatoses with recommendations regarding when to refer to a nephrologist if one suspects a relationship between the skin and kidneys or if a patient exhibits signs or symptoms of renal pathology. In **Table II**, we include the known genetic mutations with gene locus as well as a summary of the cutaneous manifestations of these nephrocutaneous genodermatoses.

NEUROFIBROMATOSIS TYPE 1

Key points

- Patients with neurofibromatosis type 1 have ocular, skeletal, neurologic, cardiovascular, neoplastic, and renal involvement in addition to their skin changes, necessitating multispecialty care coordination
- Dermatologists must be fully aware of the diagnostic skin criteria to ensure early coordination and appropriate renal evaluation

Etiology

Neurofibromatosis type 1 (NF-1), also known as von Recklinghausen disease, is an autosomal dominant or spontaneous (30-50%) disorder with an incidence of 1 in 3000 live births. This condition is caused by a deletion mutation in the *NF-1* gene located on chromosome 17, which leads to truncation of the neurofibromin protein.¹⁻³ The neurofibromin protein is a GTPase-activating protein (GAP)-related protein and plays a crucial role in the negative regulation of the Ras-mitogen-activated protein kinase (MAPK) pathway, which promotes cell survival and proliferation. Ras activity requires GTP, and neurofibromin (in conjunction with other GAPs) accelerates the hydrolysis of GTP to GDP, depriving the Ras proliferation signal of the GTP required to propagate it.⁴ In summary, neurofibromin functions as a tumor suppressor protein. The genetic pathway implicated in the pathogenesis of NF-1 is shown in **Fig 1**.

Cutaneous manifestations

Cutaneous findings in patients with NF-1 are almost universal and consist of café-au-lait macules, inguinal or axillary vault freckling, and cutaneous neurofibromas (**Fig 2**).^{1,5-7} Plexiform neurofibromas may infiltrate deeply and diffusely and occur in approximately 25% of patients with NF-1. Malignant transformation of plexiform neurofibromas into malignant peripheral nerve sheath tumors occurs in 3% to 15% of patients with NF-1.⁸ Other cutaneous findings in patients with NF-1 include glomus tumors and juvenile xanthogranulomas.

Other manifestations

Ocular complications, such as Lisch nodules (iris hamartomas), hypertelorism, and glaucoma

Table II. Summary of genetic defects and cutaneous manifestations in the spectrum of nephrocutaneous genodermatoses

Genodermatoses	Gene mutation	Gene locus	Cutaneous manifestations
Neurofibromatosis type 1	<i>NF1</i> (neurofibromin)	17q	Neurofibromas, café-au-lait macules, axillary/inguinal freckling, glomus tumors, and juvenile xanthogranulomas
Tuberous sclerosis	<i>TSC1</i> (hamartin) and <i>TSC2</i> (tuberin)	9q (<i>TSC1</i>) and 16p (<i>TSC2</i>)	Facial angiofibromas, hypomelanotic macules, connective tissue nevi, periungual fibromas, and café-au-lait macules
Beckwith-Wiedemann syndrome	Multiple	Distal arm of 11p	Hemihypertrophy, ear (helical) pits, earlobe crease, and facial nevus flammeus
von Hippel-Lindau syndrome	<i>VHL</i>	3p	Capillary malformations and café-au-lait macules
Birt-Hogg-Dubé syndrome	<i>FLCN</i> (folliculin)	17p	Fibrofolliculomas, trichodiscomas, acrochordons, and epidermoid cysts
Cowden syndrome	<i>PTEN</i>	10q	Trichilemmomas, acral keratoses, sclerotic fibromas, lipomas, inverted follicular keratoses, and facial papillomas
Hereditary leiomyomatosis and renal cell cancer	<i>FH</i> (fumarate hydratase)	1q	Piloleiomyomas and angioleiomyomas
Fabry disease	<i>GLA</i> (alfa-galactosidase A)	X	Angiokeratomas, hypohidrosis, and anhidrosis
Nail-patella syndrome	<i>LMX1B</i>	9q	Triangular lunula, absent or hypoplastic nails, skin laxity, webbing at elbows or between digits, and absence of distal dorsal phalangeal skin creases
Turner syndrome	Monosity X	X (no specific locus identified)	Congenital lymphedema, cystic hygroma, alopecia, cutis laxa, keloids, numerous melanocytic nevi, and increased risk for melanoma and pilomatricomas

may occur in patients with NF-1 in addition to a myriad of skeletal manifestations (eg, macrocephaly, sphenoid wing dysplasia, and scoliosis).⁶⁻¹⁰ Neurologic complications, including learning difficulties, seizures, or mental retardation may also be evident.^{5,8,10} Notably, patients with NF-1 are at a high risk for the development of numerous other tumors, both cutaneous (eg, juvenile xanthogranulomas and glomus tumors) and extracutaneous.^{11,12}

Renal manifestations

Though uncommon, patients with NF-1 have been reported to have a higher incidence of renal tumors, specifically Wilms tumor (nephroblastoma) and angiomyolipomas when compared to the general population.¹³⁻¹⁵ In addition, hypertension has been reported in approximately 30% of patients with NF-1, mostly essential in origin but in some patients attributable to renal artery stenosis.¹⁶

Therapy

Nephrology referral on initial presentation is imperative for any patient with NF-1 and concomitant

hypertension.¹⁰ Prompt referral is critical for imaging evaluation of possible renal artery stenosis and to prevent potential end-organ damage from uncontrolled hypertension via interventions, such as revascularization procedures. Coordination of care in patients with NF-1 should include a dermatologist, ophthalmologist, neurologist, and genetic counselor.¹⁷

TUBEROUS SCLEROSIS

Key point

- Patients with tuberous sclerosis have ocular, dental, pulmonary, neurologic, cardiovascular, and renal complications in addition to cutaneous findings necessitating multispecialty care coordination

Etiology

Tuberous sclerosis (TS), also known as Bourneville disease, is an autosomal dominant or sporadic (75%) syndrome occurring in 1 in 10,000 live births. This condition is caused by mutations in the *TSC1* (chromosome 9) or *TSC2* genes

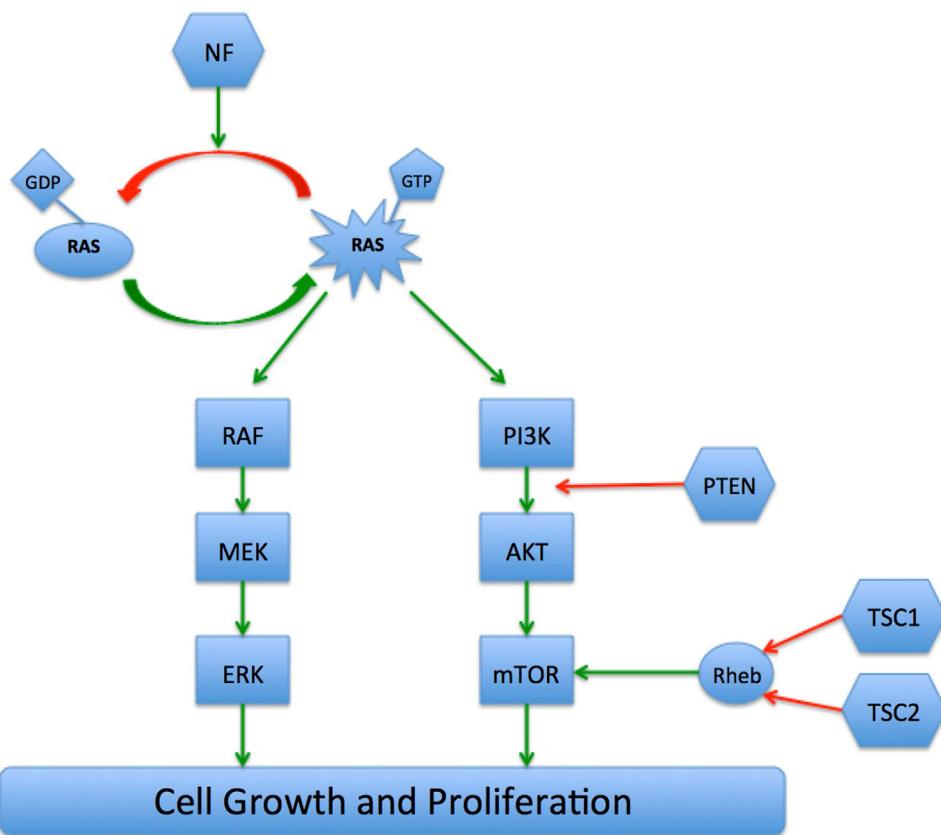


Fig 1. The neurofibromatosis 1 gene, neurofibromin protein, and Ras—mitogen-activated protein kinase pathway.



Fig 2. Neurofibromatosis type 1. Note the diffuse cutaneous neurofibromas.

(chromosome 16), which encode the proteins hamartin and tuberin, respectively. The proteins hamartin and tuberin interact to hydrolyze GTP to GDP, inhibiting activity of the small GTPase proteins Rab and Rheb. Inhibition of Rab and Rheb prohibits activation of the mechanistic target of rapamycin (mTOR) signaling pathway, which normally promotes cell growth and proliferation.¹⁸⁻²² Hamartin and tuberin are therefore tumor suppressor proteins that closely interact with one another (Fig 1).

Cutaneous manifestations

Cutaneous manifestations in TS are numerous and consist of facial angiofibromas, polygonal or confetti hypomelanotic macules, connective tissue nevi, periungual fibromas, and café-au-lait macules (Fig 3).²³⁻²⁵ Polygonal hypomelanotic macules, or “ash-leaf spots,” are the earliest manifestation and are invariably present at birth (Fig 4).

Other manifestations

Dental findings (eg, gingival fibromas and enamel pits) are extremely common, as are myocardial rhabdomyomas.^{26,27} Other less common organ system findings involve the eyes (ie, retinal hamartomas) and lungs (ie, pulmonary lymphangioleiomyomatosis).^{28,29} Neurologic associations include seizures (70-95%), subependymal nodules (>80%), cortical tubers (>90%), infantile spasms (70%), mental retardation, and intracranial calcifications.^{23,27}

Renal manifestations

Renal manifestations are common in patients with TS, with multiple and bilateral angiomyolipomas being noted in 75% to 90% of patients during

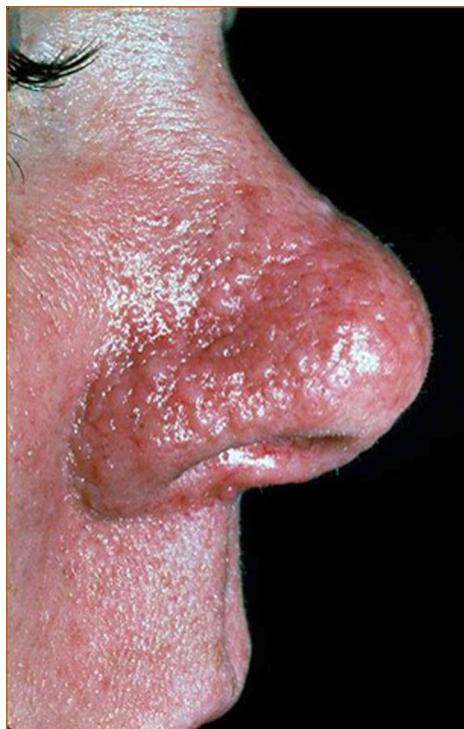


Fig 3. Tuberous sclerosis. Note the numerous facial angiofibromas.

ultrasonography. These lesions are usually asymptomatic.³⁰ Children with TS may also develop multiple renal cysts caused by a single large gene deletion of the *TSC2* gene and the contiguously located polycystic kidney disease (*PKD*) gene on chromosome 16.^{18,31} Rarely, renal cell carcinoma may develop in patients with TS.

Therapy

Referral to nephrology is essential for any patient with a new diagnosis of TS. Because of the frequent finding of renal neoplasms in these patients, an ultrasonographic evaluation should be undertaken during early childhood. While the angiomyolipomas of patients with TS are usually asymptomatic, the finding of renal cysts suggesting possible PKD may require surgical intervention to preserve renal function. Current guidelines recommend renal ultrasonography at the time of diagnosis of TS, every 1 to 3 years with no history of renal lesions, and twice yearly for patients with known angiomyolipomas.^{30,32} In addition, a multidisciplinary treatment team is essential to the long-term care of these patients.

BECKWITH-WIEDEMANN SYNDROME

Key point

- Patients with Beckwith-Wiedemann syndrome have a range of characteristic congenital features and an increased risk of multiple childhood malignancies

Etiology

Beckwith-Wiedemann syndrome (BWS) is a rare disorder of overgrowth of different structures with a complex genetic pathogenesis. The majority of cases (85%) of BWS are sporadic, with the minority being attributable to an autosomal dominant inheritance. Regardless, the syndrome is a consequence of an alteration in the distal region of the short arm of chromosome 11 (11p), which results in various genetic defects. Overactivity of the insulin-like growth factor 2 (IGF-2) gene or a defective copy of the *CDKN1C* gene (an inhibitor of cellular proliferation) have both been implicated in the pathogenesis of BWS in some patients. Other genetic and epigenetic alterations (such as aberrant DNA methylation of the *H19* gene) have also been implicated.^{33,34}

Cutaneous manifestations

Dermatologic manifestations include posterior helical pits or earlobe creases (63%) and hemihypertrophy of the trunk or limbs. Up to 56% of patients also exhibit facial nevus flammeus.³⁴⁻³⁶

Other manifestations

Infants with BWS tend to be large for gestational age and may present with hypoglycemia complicating the perinatal period. The cardinal features of BWS include postnatal overgrowth, macroglossia, cardiac defects, and anterior abdominal wall defects. In addition, patients have internal organ overgrowth, leading to hepatomegaly and nephromegaly.³⁴⁻³⁶

Renal manifestations

While most patients with BWS do not develop cancer, afflicted individuals are approximately 800 times more likely to develop certain childhood tumors, particularly Wilms tumor (nephroblastoma). The increased risk for cancer appears to be present only in childhood, with most cases occurring before 4 years of age, and is rarely seen in adulthood. Other tumors that present in children with BWS include rhabdomyosarcoma, hepatoblastoma, adrenal cortical carcinoma, neuroblastoma, and rhabdomyosarcoma. Finally, patients with BWS have an increased incidence (25%) of other nonmalignant renal pathologies, including renal cysts, hydronephrosis, caliceal diverticula, and nephrolithiasis.^{37,38}

Therapy

Because of the increased incidence of cancer in children with BWS, all children with BWS should undergo early cancer screening. Referral to nephrology is advised for screening for Wilms tumor and other renal complications. Current



Fig 4. Tuberous sclerosis. Note the hypopigmented “ash-leaf” macules.

recommendations call for abdominal ultrasonography every 3 to 4 months until 7 to 8 years of age to evaluate for Wilms tumor and hepatoblastoma. Because both Wilms tumor and hepatoblastoma are curable if diagnosed early, prompt and regular screening is critical to the management of these patients.³⁹

VON HIPPEL–LINDAU SYNDROME

Key point

- **von Hippel–Lindau syndrome is a multi-system disorder with cutaneous findings in a small minority of patients at risk for multiple different malignancies, requiring early diagnosis to improve patient outcomes**

Etiology

von Hippel–Lindau (VHL) syndrome is a rare autosomal dominant (80% of cases) condition that arises because of a mutation in the VHL tumor suppressor gene located on chromosome 3. A minority (20%) of cases occur because of de novo mutations.^{40,41} The *VHL* gene product is an ubiquitin ligase involved in the regulation of a protein called hypoxia inducible factor 1–alfa (HIF1 α). When the *VHL* gene is mutated, a defective *VHL* gene product is unable to bind to and inhibit the activity of HIF1 α . Unregulated HIF1 α activates the transcription of numerous genes, including vascular endothelial growth factor, platelet-derived growth factor B, erythropoietin, and other genes involved in glucose uptake and metabolism.^{42,43} In concert, these factors facilitate neoangiogenesis and tumorigenesis.⁴⁴

Cutaneous manifestations

Patients with VHL uncommonly present with dermatologic manifestations, which occur in <5% of patients with VHL, and include capillary malformations, usually of the head and neck (Fig 5). Patients with VHL may also have café-au-lait macules.⁴⁵



Fig 5. von Hippel–Lindau syndrome. Note the capillary malformation of the lower lip.

Other manifestations

Patients with VHL usually present by the fourth decade of life, showing primarily signs and symptoms of visceral or central nervous system tumors, both benign and malignant. Central nervous system tumors vary in type and include cerebellar, medullary, or spinal cord hemangiomas or hemangioblastomas in addition to endolymphatic sac tumors. Patients frequently develop retinal hemangioblastomas, which may result in visual impairment or blindness if untreated. Other tumors seen in this patient population include pheochromocytoma, paraganglioma, and adrenal carcinoma. Pancreatic cysts may also develop, as can epididymal cystadenomas in men.⁴⁶

Renal manifestations

Renal manifestations include renal clear cell carcinoma and renal cysts, which occur in 24% to 60% of patients with VHL.⁴⁶ These tumors and cysts are often multiple and bilateral, and may remain asymptomatic for years. Some of these patients have numerous cysts, occasionally leading to a misdiagnosis of autosomal dominant polycystic kidney disease. Initial presenting symptoms may include microscopic or gross hematuria.⁴⁵

Therapy

Because of the increased risk of central nervous system and visceral malignancies, all patients with suspected or confirmed VHL require multiple referrals for cancer screening. Referral to nephrology is essential, because initial and subsequent ultrasonographic examinations of the abdomen are necessary to detect renal tumors or cysts in young patients. However, because of the low sensitivity of abdominal ultrasonography in detecting renal lesions, contrast-enhanced computed tomography scanning is recommended beginning in the mid-teenage years in patients with VHL. In addition,

measurement of serum catecholamine and urinary vanillylmandelic acid levels is recommended.⁴⁷ Finally, renal transplantation may be considered for patients with VHL.

BIRT-HOGG-DUBÉ SYNDROME

Key point

- **Birt-Hogg-Dubé syndrome is a hereditary disorder characterized by the presence of numerous follicular hamartomas in conjunction with an increased risk for developing renal cell carcinoma**

Etiology

Birt-Hogg-Dubé (BHD) syndrome is an autosomal dominant disorder caused by a mutation in the BHD (*FLCN*) gene, located on chromosome 17p.⁴⁸ This gene encodes folliculin, a tumor suppressor protein whose function remains to be fully elucidated. Folliculin has been shown to interact with another protein, folliculin-interacting protein (FNIP1). Together, folliculin and its interacting partner FNIP1 appear to modulate energy and nutrient sensing as downstream effectors of the mTOR and AMP-activated protein kinase (AMPK) signaling pathways.^{49,50}

Cutaneous manifestations

BHD is defined by a triad of benign cutaneous hamartomas, including fibrofolliculomas, trichodiscomas, and acrochordons. Clinically, patients with BHD manifest by the fourth decade of life with numerous (often hundreds) benign follicular hamartomas on the central face, neck, and upper aspect of the trunk (Fig 6). Despite often being described separately in the literature, fibrofolliculomas and trichodiscomas represent the same tumor cut in different planes of section, showing either epithelial or stromal elements, respectively. Patients with BHD may also develop multiple epidermoid cysts.

Other manifestations

Oral lesions have been noted in this patient population and described as small, discrete mucosa-colored or white papules on the lips, gingiva, tongue, or buccal mucosa.^{51,52} In addition to cutaneous and oral manifestations, patients with BHD are at risk for spontaneous pneumothorax, which results from the presence of pulmonary cysts affecting >80% of patients with BHD syndrome.⁵³

Renal manifestations

Up to 30% of patients with BHD syndrome develop renal tumors of various subtypes that are



Fig 6. Birt-Hogg-Dubé syndrome. Note the numerous facial fibrofolliculomas.

often multiple and bilateral. Development of renal oncocytomas, chromophobe renal cell carcinomas, or a mixed type is characteristic of BHD syndrome. These histologic variants of RCC are otherwise rare. Patients may also develop multiple renal cysts.⁵⁴

Therapy

Management of patients with BHD syndrome requires a multispecialty approach. It is recommended that all patients newly diagnosed with BHD syndrome have a chest radiograph, abdominal computed tomography scan, and renal ultrasonography. Appropriate referral to pulmonology and nephrology is recommended. Thereafter, patients require lifelong regular screening for renal cancer. Firm guidelines regarding the frequency of screening have yet to be fully established.^{52,55}

COWDEN SYNDROME

Key point

- **Cowden syndrome is a genetic disorder characterized by the presence of multiple hamartomatous tumors of the skin, soft tissues, and mucosa coupled with an increased risk of carcinomas of multiple internal organs**

Etiology

Cowden syndrome (CS), also known as multiple hamartoma syndrome, is a rare autosomal dominant condition caused by mutations in the phosphatase and tensin homolog (*PTEN*) tumor suppressor gene located on chromosome 10q.⁵⁶ The *PTEN* protein is a phosphatase enzyme that functions in cell cycle regulation and apoptosis. The *PTEN* gene product suppresses activity of the phosphatidylinositol 3-kinase (PI3K)/mTOR cellular proliferation pathway (Fig 1). Loss of *PTEN* suppressor function results in unregulated cell cycle propagation and tumorigenesis.^{56,57}



Fig 7. Cowden syndrome. Note the characteristic cobblestone tongue.

Cutaneous manifestations

Cutaneous findings of CS usually present in the second to third decade of life and include facial trichilemmomas, acral (often palmoplantar) punctate keratoses, and other nonspecific keratotic papules (Figs 7 and 8). The presence of multiple sclerotic fibromas of the skin is a relatively specific finding in CS. Other cutaneous features include lipomas, angioliomas, vascular anomalies, acrochordons, and inverted follicular keratoses.⁵⁷⁻⁶⁰

Other manifestations

Oral involvement may occur with the presence of numerous, often coalescing, papillomas creating a cobblestone appearance of the tongue and oral mucosa.⁶¹ In addition to the mucocutaneous findings, approximately two-thirds of CS patients develop thyroid disease, including goiters, adenomas, and carcinomas (5-10%). Breast pathology is also common in female patients with CS and includes both benign conditions (eg, fibrocystic change, fibroadenomas, and ductal papillomas) and carcinomas ($\leq 50\%$ of female patients). Gastrointestinal tract involvement is characterized by multiple hamartomatous polyps affecting the esophagus, stomach, small bowel, large intestine, or anus. Fortunately, malignant transformation of polyps is extremely rare. Other neoplastic developments reported in patients with CS include benign ovarian cysts, uterine leiomyomas, and endometrial carcinoma.⁶² Craniomegaly is a common skeletal manifestation of CS, occurring in the majority of patients, and may less commonly be accompanied by other skeletal anomalies, including high-arched palate, kyphoscoliosis, pectus excavatum, and syndactyly.⁵⁹

Renal manifestations

Patients with CS have an approximate 33% lifetime risk for developing renal cell carcinoma. Varying histologic subtypes of renal cell carcinoma

have been associated with CS, but the papillary histologic subtype appears to be most common. Transitional cell carcinoma of the renal pelvis and ureter has also been associated with CS.^{63,64}

Therapy

Appropriate management of patients with CS requires diligent tumor surveillance by multiple specialists. Surveillance recommendations for renal tumors include yearly imaging and urinalysis with urine cytology. Referral to nephrology is necessary to coordinate annual renal imaging with either ultrasonography or magnetic resonance imaging.^{63,64}

HEREDITARY LEIOMYOMATOSIS AND RENAL CELL CANCER (REED SYNDROME)

Key point

- Hereditary leiomyomatosis and renal cell cancer is a heritable syndrome defined by the triad of cutaneous leiomyomas, uterine fibroids, and renal cell carcinoma

Etiology

Heredity leiomyomatosis and renal cell cancer (HLRCC), also known as Reed syndrome, is an autosomal dominant condition caused by mutations in the fumarate hydratase (*FH*) gene located on chromosome 1q. *FH* is an enzyme that catalyzes the conversion of fumarate to malate in the tricarboxylic acid cycle.⁶⁵ The *FH* gene functions as a tumor suppressor gene, and defects in *FH* activity promote tumorigenesis via multiple pathways. With defective *FH* activity, fumarate accumulates in cells and inhibits breakdown of hypoxia inducible factor (HIF), activating hypoxia pathways. Transcription factor HIF increases expression of angiogenesis regulated genes, promoting tumorigenesis. Increased HIF activity in cells may also induce free radical formation.⁶⁶ In addition, *FH* activity has been shown to play a crucial role in protecting cells from DNA damage, especially DNA double-strand breaks.⁶⁷ This discovery further underscores *FH* gene function as a tumor suppressor.

Cutaneous manifestations

The primary characteristics of HLRCC include cutaneous leiomyomas, uterine leiomyomata (ie, fibroids), and renal cell carcinoma (RCC), primarily of the papillary subtype. Cutaneous tumors can be of the piloleiomyoma or angioleiomyoma subtype and usually present during the second to third decades of life, affecting approximately 75% of patients with HLRCC. The tumors are described as skin-colored to brown, firm cutaneous papules or nodules and tend to increase in size and number with age (Fig 9). The

lesions, usually concentrated on the trunk and extremities, may be painful or sensitive to light touch or cold temperature.⁶⁵

Other manifestations

Uterine leiomyomas are essentially universal in women with HLRCC and present at a younger age and in larger numbers in these individuals compared with the general population. The large and numerous uterine fibroids in HLRCC patients often lead to irregular and/or heavy menstruation and pelvic pain. These symptoms may lead to hysterectomy in young women with HLRCC (often before 30 years of age). Of note, while numerous cases of uterine leiomyosarcoma have been reported in women with HLRCC, the causal association of *FH* gene mutations with the development of uterine leiomyosarcoma in these patients has yet to be validated.⁶⁸

Renal manifestations

Patients with HLRCC are at an increased risk for developing RCC, particularly of the type II papillary histology. While the majority of renal tumors in patients with HLRCC are unilateral and solitary, multiple tumors have been reported. RCC has been estimated to occur in only 10% to 16% of patients with HLRCC. However, the RCC in these patients is often aggressive and fatal. In addition to type II papillary RCC, patients with HLRCC may also develop the tubulopapillary histologic subtype or collecting duct carcinoma of the kidney.^{65,68}

Therapy

All patients diagnosed with HLRCC require baseline renal ultrasonography and abdominal computed tomography scans with contrast to evaluate for renal tumors. Immediate referral to nephrology is also recommended. Because renal tumors in patients with HLRCC are often highly aggressive, total nephrectomy should be strongly considered in patients with any detectable renal mass. Yearly abdominal magnetic resonance imaging scans are recommended for long-term surveillance of these patients.⁶⁵

FABRY DISEASE

Key point

- **Fabry disease is an X-linked genetic disorder characterized by a lysosomal enzyme deficiency that leads to the accumulation of toxic metabolic products in cells and, if untreated, to multiorgan system damage**



Fig 8. Cowden syndrome. Note the multiple facial trichilemmomas/papillomas.

Etiology

Fabry disease (FD) is a rare genetic lysosomal storage disease that is inherited in an X-linked recessive manner. This disease is caused by mutations in the *GLA* gene, which encodes the enzyme alfa-galactosidase A. Deficiency of alfa-galactosidase A causes an upstream glycosphingolipid, globotriaosylceramide (GL-3), to accumulate within the lysosomes of cells in various organ systems. GL-3 is toxic, triggering cellular dysfunction and eventually cell death within multiple internal organs, resulting in tissue ischemia, fibrosis, and impairment of proper organ function.⁶⁹ While men with the disease (hemizygous) typically experience a severe phenotype, incomplete penetrance is observed in heterozygous females, whose presentation may range from asymptomatic to severe. The variability in female phenotype is thought to be caused by X-inactivation patterns during embryonic development.⁷⁰

Cutaneous manifestations

FD affects multiple organ systems, with symptoms often appearing in early childhood. Skin manifestations include the widespread development of angiokeratomas (ie, angiokeratoma corporis diffusum), particularly on the lower trunk, groin region, and upper aspects of the thighs ("bathing trunk" distribution). These lesions may occur throughout the body surface, but usually spare the face, scalp, and ears (Fig 10). Other manifestations include hypohidrosis or, less commonly, anhidrosis.⁷¹

Other manifestations

Localized pain to the extremities (acroparesthesias) and the gastrointestinal tract can be an early finding in FD and is thought to be caused by peripheral nerve fiber and small bowel ischemia, respectively. Other peripheral or central neuropathies may occur. Accumulation of glycosphingolipid in cardiac muscle cells can lead to hypertrophic or



Fig 9. Hereditary leiomyomatosis and renal cell carcinoma. Note the numerous cutaneous leiomyomas on the trunk.

ischemic cardiomyopathy and heart failure. Also, patients with FD are at increased risk for cerebrovascular accidents, in addition to hearing loss and tinnitus. Ocular involvement in the form of cornea verticillata (vortex keratopathy) leads to characteristic clouding of the cornea (whorled corneal opacity), which may be a presenting feature in otherwise asymptomatic patients.⁷² This keratopathy does not affect visual acuity. Other ocular findings include conjunctival aneurysms, cataracts, macular edema, optic atrophy, and retinal vasculopathy.^{69,70}

Renal manifestations

Renal complications of FD are common and can lead to chronic kidney disease (CKD) or, ultimately, to end-stage renal disease (ESRD). Progressive renal failure results from glycosphingolipid accumulation within renal glomeruli and renal tubules. The distal tubules are preferentially affected, leading to decreased urinary concentrating ability and polyuria.⁷³ Proteinuria is often the presenting sign of renal involvement in patients with FD. ESRD may occur by the third decade of life and is the most common cause of mortality in patients with FD.^{69,70}

Therapy

The cornerstone of treatment for FD is enzyme replacement therapy, which has been shown to prevent end-organ damage in patients who receive early treatment. All patients with a diagnosis of FD should be referred immediately to nephrology for evaluation. Measurement of 24-hour urine protein levels is recommended at baseline and at regular intervals (every 12 months at the least) to monitor for renal disease.^{72,74}

NAIL–PATELLA SYNDROME

Key point

- Nail–patella syndrome is an autosomal dominant genetic disorder characterized by a tetrad of nail dystrophy, hypoplasia or

absence of the patellae, ocular defects, and glomerulonephritis

Etiology

Nail–patella syndrome (PTS), also known as hereditary onycho-osteodysplasia or Fong disease, is an autosomal dominant disorder caused by mutations in the gene encoding the LIM homeobox transcription factor 1-beta (LMX1B), which is located on chromosome 9q. The LMX1B transcription factor has been shown to play a crucial role in dorsoventral limb patterning during embryonic development. In addition, the LMX1B transcription factor plays an essential role in development of the anterior segment of the eye. Finally, via regulation of type IV collagen synthesis, the LMX1B transcription factor is vital in the development of the glomerular basement membrane of the kidney.^{75,76}

Cutaneous manifestations

The primary nail changes in NPS include the presence of a triangular lunula and absent or hypoplastic nails. The most prominently involved nail is the thumbnail, followed by those of the more radially located digits. An individual nail is usually more severely affected on its ulnar side, with a diminishing gradient of dystrophy towards the radial aspect of each involved nail. Cutaneous features of NPS may include general laxity of the skin, webbing of the skin of the elbows or between the digits, and absence of skin creases on the dorsal aspects of the distal interphalangeal joints.^{77,78}

Other manifestations

Skeletal manifestations of the syndrome are myriad, and include absent or hypoplastic patellae, dysplasia of the radial head, and iliac crest exostoses (“iliac horns”), which are pathognomonic. In children, the diagnosis of NPS is often confirmed by observation of “iliac horns” on pelvic radiographs. Arthrodysplasia of the elbow joint is present in the majority of cases. Dysplasia or thickening of the scapula and scoliosis may also be observed. Glaucoma, cataracts, and heterochromia of the irides may also be present in this syndrome. Hyperpigmentation of the pupillary margin of the iris (“Lester iris”) occurs in approximately half of cases.^{77,78}

Renal manifestations

Renal findings are among the most clinically significant features of this condition. Patients with NPS are often affected by glomerulonephritis, with urinary findings including proteinuria, hematuria, or urinary casts. Nephropathy develops in



Fig 10. Fabry disease. Note the angiokeratoma corporis diffusum with affected genitalia.

approximately 40% to 60% of patients, with progressive CKD and ESRD occurring in 5% to 15% of cases. The pathologic nature of renal disease in patients with NPS varies, ranging from focal and segmental glomerulosclerosis to proliferative crescentic glomerulonephritis. The only consistent histopathologic finding among patients is focal thickening of the glomerular basement membrane. Overall, the presence and prognosis of renal disease in NPS patients is unpredictable.^{77,79}

Therapy

At initial diagnosis, all patients with NPS should receive urinalysis to examine for proteinuria or hematuria, the earliest signs of nephropathy. Early nephrology referral is advised to allow for patients to be followed for progression of renal disease.⁷⁹

TURNER SYNDROME

Key point

- **Turner syndrome is a chromosomal disorder characterized by congenital lymphedema and renal malformations, along with other organ system findings**

Etiology

Turner syndrome (TS) is caused by a chromosomal aberration in which the affected individual has monosomy of the X chromosome (genotype 45, XO). This syndrome is one of the most common chromosomal abnormalities, occurring in approximately 1 in 2000 live female births. Mosaicism and structural abnormalities in or partial deficiency of the X chromosome may account for variations in the clinical phenotype. Approximately 40% of patients with TS exhibit mosaicism. Several genetic loci on the X chromosome have been implicated in TS. Loss of the long arm of the X chromosome (Xq), which contains the short stature homeobox gene, results in short stature and ovarian failure. Loss of the short arm of the X chromosome (Xp) produces the full phenotype.⁸⁰

Cutaneous manifestations

Patients with TS may develop multiple mucocutaneous anomalies. Congenital lymphedema is perhaps the most characteristic cutaneous finding of TS, often presenting with swollen hands and feet at birth and usually resolves by 2 years of age. Macrocystic lymphatic malformations (cystic hygroma) represent collections of large, interconnected lymphatic cysts lined by endothelium and may occur in patients with TS. These lesions present as large, soft, translucent, subcutaneous masses located on the neck, axilla, and lateral chest wall. Other manifestations include a low posterior hairline margin, numerous melanocytic nevi, hyperconvex nails, cutis laxa, and tendency to form keloids. These patients often have frontal alopecia and an increased risk for developing alopecia areata. Patients with TS also have an increased risk for developing melanoma and pilomatricomas.⁸¹

Other manifestations

Extracutaneous findings include short stature, cardiovascular defects (especially aortic coarctation), a webbed neck, a “shield-like” shape to the chest with widely spaced nipples, and primary amenorrhea with absence of secondary sexual characteristics. In addition, patients may develop sensorineural hearing loss and autoimmune hypothyroidism.^{80,82}

Renal manifestations

Approximately one-third of women with TS have developmental renal malformations. These malformations include a single, horseshoe-shaped kidney (often referred to as “horseshoe kidney”), collecting system malformations, or malrotation of the kidneys. These malformations can predispose patients to recurrent urinary tract infections (caused by obstruction). In addition, hypertension is common in patients with TS, even in the absence of recognizable malformations, and should be regularly screened for in these patients.^{80,82}

Therapy

Early identification of the clinical manifestations of this syndrome is crucial to allow for early referral to specialists, including nephrology, cardiology, and endocrinology. Patients with TS require ultrasonography of the kidneys and the renal collecting system at diagnosis. Growth hormone has been used in some patients to treat short stature.⁸³

In conclusion, many seemingly isolated cutaneous findings can be associated with significant underlying renal disease in the setting of inherited

nephrocutaneous syndromes. It is essential that dermatologists have a thorough understanding of these disorders. Dermatologists must play a central role in identifying patients with these conditions and appropriately referring them to nephrologists when necessary. Part II of this continuing medical education article reviews the inflammatory conditions with relevant renal manifestations as well commonly used therapeutic agents with nephrocutaneous side effects or important renal function considerations.

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The spectrum of nephrocutaneous diseases and associations

Inflammatory and medication-related nephrocutaneous associations

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Learning objectives

After completing this learning activity, participants should be able to recognize the important relationship between the skin and the kidney with respect to pharmacology and understand and manage the complex relationship between the skin and kidneys with respect to systemic medications.

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There are a significant number of dermatoses associated with renal abnormalities and disease, and dermatologists need to be keenly aware of their presence in order to avoid overlooking important skin conditions with potentially devastating renal complications. This review discusses important nephrocutaneous disease associations and recommendations for the appropriate urgency of referral to nephrology colleagues for diagnosis, surveillance, and early management of potential renal sequelae. Part II of this 2-part continuing medical education article addresses inflammatory and medication-related nephrocutaneous associations. (J Am Acad Dermatol 2016;74:247-70.)

Key words: antihypertensive medication; autoimmune; dermatology; genetic; genodermatoses; immunosuppression; inflammatory; medication side effects; nephrocutaneous; nephrology; renal transplantation.

INFLAMMATORY CAUSES OF NEPHRO CUTANEOUS DISEASE

In this first section of part II, we discuss the cutaneous and renal findings associated with numerous inflammatory dermatoses. Table I is a summary of the cutaneous and renal findings

associated with the nephrocutaneous inflammatory syndromes with recommendations regarding appropriate referral to a nephrologist for work-up and management of potential renal complications. Clinical presentation of the patient should also be taken into consideration.

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Table I. Inflammatory nephrocutaneous diseases including associated cutaneous and renal manifestations and referral considerations

Disease	Cutaneous findings	Renal findings	Referral
Nephrogenic systemic fibrosis	Firm dermal plaques, cobblestone appearance, joint contractures, and skin induration	Renal failure (causative) with subsequent administration of gadolinium contrast	Potentially urgent
Henoch-Schönlein purpura	Palpable purpura and petechiae	Immunoglobulin A nephropathy, vasculitis, nephrotic syndrome, and end-stage renal disease	As clinically indicated
Granulomatosis with polyangiitis and microscopic polyangiitis	Palpable purpura, ulceration, tender nodules, and focal necrosis	Focal and segmental, necrotizing and crescentic, or pauciimmune glomerulonephritis and vasculitis	Potentially urgent
Polyarteritis nodosa	Purpura, livedoid lesions, subcutaneous nodules, and necrotic ulcers	Renal arterial hypertension, renal microaneurysms, and renal infarction	Potentially urgent
Systemic lupus erythematosus	"Butterfly" rash, photosensitivity, discoid plaques, alopecia, and oral or nasal ulcers	Immune complex-mediated glomerulonephritis and end-stage renal disease	As clinically indicated
Cryoglobulinemia	Purpura, acrocyanosis, ulcerations, necrosis, and livedo reticularis	Thrombotic vasculopathy and glomerulonephritis	Potentially urgent
Sarcoidosis	Dermal papules/plaques, nodules, ulcers, erythema nodosum, hypomelanotic patches, erythroderma, and ichthyosiform lesions	Granulomatous nephritis, nephrolithiasis, and renal failure	As clinically indicated
Systemic sclerosis	Raynaud phenomenon, sclerodactyly, scleroderma, "salt and pepper" pigmentation, and ventral pterygium	Hypertension, scleroderma, and renal crisis with acute renal failure	Potentially urgent

Nephrogenic systemic fibrosis

Clinical manifestations. Nephrogenic systemic fibrosis (NSF) is a recently identified fibrosing disorder that occurs in patients with severe kidney failure, either chronic or acute, the vast majority of whom have been exposed to gadolinium-based contrast agents.¹ The pathophysiology of this condition involves tissue deposition of gadolinium, which results in a marked expansion and fibrosis of the dermis in association with CD34⁺ and procollagen 1⁺ fibrocytes.² All patients appear to have skin involvement, which may include bilateral and symmetrical patterned plaques in the skin, cobblestone appearance of the skin, joint contractures, and marked induration/peau d'orange of the skin.³ Affected individuals may also develop erythematous to purple-brown superficial patches with an irregular advancing edge or discrete dermal papules (Fig 1). Yellow scleral plaques may also be present in this patient population. The disease often involves deeper structures, such as muscle, fascia, the lungs, and the heart.

Diagnosis. The diagnosis of NSF is based on histopathologic examination of a biopsy specimen obtained from an involved site. There are no laboratory tests or imaging studies specific for this



Fig 1. Nephrogenic systemic fibrosis. Note the induration, thickening, and hardening of the lower extremities with hyperpigmentation.

disease. Affected patients often have elevations in serum C-reactive protein, serum ferritin, and erythrocyte sedimentation rate.⁴ The histologic findings of NSF include increased spindled and epithelioid cells, CD34⁺ spindled or epithelioid cells with dendritic processes on either side of elastic fibers (so-called "tram-tracking"), and the presence of fine and ropey collagen surrounded by clefts.³

Therapy. NSF has a chronic and unremitting course in most patients, with a high mortality rate.⁴



Fig 2. Henoch–Schönlein purpura. Note the palpable purpuric lesions on the lower extremities of this patient.

Complete remissions have been reported, primarily in patients who had improvement or resolution of their renal failure. Several therapies have been attempted for this condition, including extracorporeal photopheresis, plasmapheresis, sodium thiosulfate, alefacept, and ultraviolet A light phototherapy, with variable clinical improvement. However, to date, there is no proven, highly effective medical therapy for NSF other than renal transplantation or recovery of the acute kidney injury.³

Henoch–Schönlein purpura

Clinical manifestations. Henoch–Schönlein purpura (HSP), also known as immunoglobulin A (IgA) vasculitis, is the most common form of systemic vasculitis in children, although the disease can occasionally be diagnosed in adults. The clinical manifestations typical of HSP include palpable purpura in the absence of thrombocytopenia, transient or migratory oligoarticular arthritis or arthralgias, nonspecific abdominal pain, and renal disease.⁵ The classic rash often begins as erythematous, macular, or urticarial wheals that later coalesce into the typical petechial and palpable purpuric lesions, often located on the face, trunk, and the lower extremities (Fig 2). Joint involvement is seen in $\leq 75\%$ of patients. Arthritis usually affects joints of the lower extremities, such as the knees and ankles, and less commonly involves smaller joints of the hands and feet. No permanent joint damage or deformities occur. Abdominal pain, seen in 60% to 70% of patients, is colicky in nature and is frequently accompanied by nausea, vomiting, constipation, or diarrhea. Occasionally, gastrointestinal bleeding may occur.⁶

Renal manifestations. Renal disease is more prevalent in older children and adults. It most commonly presents with microscopic hematuria and little to no proteinuria, and is histologically indistinguishable from IgA nephropathy when reviewing kidney biopsy specimens. In a minority of patients, nephrotic range proteinuria with or

without the nephrotic syndrome, hypertension, or progressive renal failure may occur, which can ultimately lead to end-stage renal disease (ESRD).

Pathology. Skin biopsy specimens of purpuric lesions in patients with HSP reveal an immune complex-mediated leukocytoclastic vasculitis with IgA and C3 deposition in the small vessels, primarily the postcapillary venules. There is often a neutrophilic infiltration around the vessel and in the vessel walls. During the acute phase, there is elevation in the serum levels of IgA and proinflammatory cytokines. Renal biopsy specimens characteristically show a mesangioproliferative glomerulonephritis on light microscopy. Immunofluorescence microscopy is often positive for IgA, IgG, and C3 deposition. In severe cases, a crescentic glomerulonephritis may be present.

Therapy. The management of HSP remains controversial and depends primarily on the clinical judgment of the treating physician. In general, adults have a worse prognosis, as do patients with renal, pulmonary, or gastrointestinal involvement. Accordingly, these patients are generally treated more aggressively. Proposed treatment regimens include corticosteroids, azathioprine, cyclophosphamide, cyclosporine, mycophenolate mofetil, and rituximab.⁷ Significant portions of cases, especially in children, are self-limited, while others periodically do recur and result in progressive organ damage.

Granulomatosis with polyangiitis and microscopic polyangiitis

Clinical manifestations. Granulomatosis with polyangiitis (GPA; formerly Wegener granulomatosis) and microscopic polyangiitis (MPA) are antineutrophil cytoplasmic antibody (ANCA)-associated clinical syndromes that are classified as small-vessel vasculitides.⁸ GPA and MPA typically occur in older adults, affect both sexes equally, and are more common in whites. Patients often present with fever, malaise, anorexia, weight loss, and migratory arthralgias. Both may have pulmonary and renal involvement manifested by the presence of cough, dyspnea, hemoptysis, pleuritic chest pain, hematuria, and subnephrotic range proteinuria. Sinus and upper airway involvement is more common in GPA patients. Cutaneous manifestations are nonspecific and occur in about 50% of these individuals, usually presenting as lower extremity purpura occasionally with focal necrosis, ulceration, or tender nodules.

Pathology. Histologically, small-vessel vasculitis is characterized by necrotizing inflammation of multiple small diameter arteries and veins, particularly venules and capillaries. Skin biopsy specimens reveal nonspecific leukocytoclastic vasculitis. Renal

biopsy specimen findings are similar in GPA and MPA, and range from a focal and segmental glomerulonephritis to a diffuse, necrotizing and crescentic glomerulonephritis. Patients with GPA may rarely show granulomatous changes as well. Few to no immune complex deposits in the glomeruli on both immunofluorescence and electron microscopy are noted in the majority of renal biopsy specimens.

Therapy. Therapy for patients with GPA and MPA is influenced by multiple factors, including the severity of the vasculitis, the presence of internal organ involvement, and the overall medical condition of the patient. Typically, there are two components to therapy: achieving remission with initial immunosuppressive therapy followed by maintenance immunosuppression to prevent relapse. Initial treatment often includes high-dose oral glucocorticoids in combination with either cyclophosphamide or rituximab.⁹ Maintenance immunosuppression is highly variable, and should take into account the potential side effects of immune-modulating drugs and their effectiveness in preventing a relapse. In an ideal situation, medications are given at the lowest possible dose needed to maintain remission.

Polyarteritis nodosa

Clinical manifestations. Polyarteritis nodosa (PAN) is a primary systemic necrotizing vasculitis predominantly targeting medium-sized arteries, which are defined as the main visceral arteries and their branches.¹⁰ Small arteries are less commonly involved, and arterioles, capillaries, and venules are characteristically spared.¹⁰ This syndrome is typically ANCA-negative and is not associated with glomerulonephritis.¹¹ PAN may be triggered by viral infections, particularly hepatitis B virus, but most cases are idiopathic.¹¹ PAN has become an increasingly rare disease because of widespread vaccination against the hepatitis B virus. PAN is a multisystem disease that can involve the skin, peripheral nerves, gastrointestinal tract, kidneys, heart, and the central nervous system. Patients often experience nonspecific constitutional symptoms, such as malaise, weight loss, myalgias, and arthralgias. Mononeuritis multiplex is the most common neurologic manifestation of this disease and may initially manifest as foot drop. Cutaneous features include palpable purpura, livedo reticularis, subcutaneous nodules, and necrotic ulcerations (Fig 3).¹¹ Subcutaneous nodules are often painful, occurring individually or in groups distributed along the course of blood vessels. The overlying epidermis may appear normal or slightly erythematous. These nodules are most frequently located on the lower legs and may



Fig 3. Polyarteritis nodosa. Note the livedo reticularis on the back of this patient.

pulsate. Ecchymoses of fingers and toes may also be present.¹²

Renal manifestations. Renal disease in patients with PAN is usually caused by the rupture of renal microaneurysms leading to tissue infarction or hematoma formation. Hypertension is common because of the involvement of intrarenal arteries. There are no specific laboratory tests for PAN, but inflammatory markers, such as erythrocyte sedimentation rate and C-reactive protein, are commonly elevated. Renal angiography may reveal irregular perfusion with arterial stenosis and microaneurysms.¹¹

Pathology. Histopathology reveals medium-sized vessel vasculitis with a surrounding mixed inflammatory infiltrate, including lymphocytes, macrophages, and some neutrophils and eosinophils. Fibrinoid necrosis is often seen in active lesions, while advanced lesions feature intimal hyperplasia and diffuse fibrotic changes.¹¹ Severe vessel wall injury can ultimately result in the formation of microaneurysms.

Therapy. The level of evidence supporting treatment decisions in PAN is low, with existing randomized clinical trials including a mixed cohort of patients.¹¹ Clinicians often consider the degree of organ involvement and the progression of the disease as a guide to the level of aggressiveness in therapy. In milder cases, oral corticosteroids alone may be sufficient to obtain and maintain a remission. In patients with severe organ involvement or rapid disease progression, an additional immunosuppressive agent is often added, the selection of which frequently depends upon the patient's individual clinical scenario. In patients with hepatitis B-associated vasculitis, antiviral therapy, such as lamivudine or adefovir, can be added along with plasma exchange.¹¹

Systemic lupus erythematosus

Clinical manifestations. Systemic lupus erythematosus (SLE) is a chronic inflammatory disease



Fig 4. Systemic lupus erythematosus. Note the periumgual/cuticular telangiectases in this patient.

of autoimmune etiology that frequently affects the skin, joints, kidneys, lungs, nervous system, and serous membranes, but can also involve other organ systems in the body. Cytopenias, thrombophilia, lymphadenopathy, and splenomegaly are also commonly present. Immune system aberrations, as well as genetic, hormonal, and environmental factors, contribute to the expression of organ damage.¹³ The production of a range of antinuclear antibodies is a prominent feature of this disease. Women are significantly more likely to be affected (10:1) than are men.¹⁴ SLE has a variable clinical course, and patients often have periods of remission interspersed with acute relapses. SLE patients commonly present with fever, fatigue, weight loss, musculoskeletal complaints, migratory arthralgias, or frank arthritis. Skin involvement is common, and includes the hallmark erythematous “butterfly rash” over the cheeks and nose, sparing the nasolabial folds. In addition, classic cuticular telangiectasias and purpuric lesions and erythematous patches between the interphalangeal joints are frequently seen (Fig 4). Photosensitivity is also common. Less frequent dermatologic manifestations include discoid lesions, alopecia, and painless oral or nasal ulcers.

Renal manifestations. Renal involvement occurs in $\leq 50\%$ of patients with SLE during the course of their disease. In these affected individuals, the urine analysis is often abnormal, with proteinuria, cellular casts, and white and red blood cells being variably present. Renal histology is quite variable, ranging from minimal abnormalities to severe proliferative or crescentic glomerulonephritis, which may lead to scarring and ESRD. Immunofluorescence microscopy often reveals widespread immune complex deposits in the subepithelial, subendothelial, and mesangial areas of the glomerulus.

Therapy. Patients with SLE are potentially treated with a variety of different agents, determined in large part by the severity of the disease and the function of the involved organ systems.¹³ These



Fig 5. Cryoglobulinemia. Lower extremity purpura in a patient with cryoglobulinemia.

agents include, but are not limited to, nonsteroidal antiinflammatory drugs, antimalarial agents, glucocorticoids, and immunosuppressive drugs, such as cyclophosphamide, azathioprine, methotrexate, and mycophenolate mofetil.¹³ The treating clinician must balance the effectiveness of these therapeutic agents with their potential, and sometimes severe, side effects. In addition, response to therapy is highly variable among different individuals, and multiple different agents are often attempted until the best approach is established.

Cryoglobulinemia

Etiology. Cryoglobulins are immunoglobulins that precipitate in vitro at temperatures $<37^{\circ}\text{C}$ and redissolve with rewarming. Cryoglobulinemia refers to the presence of cryoglobulins in serum. Monoclonal cryoglobulinemia (type I) involves a single type of monoclonal immunoglobulin (Ig). Mixed cryoglobulinemia involves a mixture of either polyclonal IgG with monoclonal IgM (type II) or of polyclonal IgG with polyclonal IgM (type III). Both monoclonal and polyclonal IgM have rheumatoid factor activity. Type I cryoglobulinemia is often associated with an underlying lymphoproliferative disorder and tends to result in a hyperviscosity syndrome. Type II and III cryoglobulinemia generally result from a chronic inflammatory state, such as systemic lupus or Sjögren syndrome or are the result of a viral infection, such as hepatitis C.¹⁵

Clinical manifestations. The clinical manifestations of these conditions depend on the type of cryoglobulinemia present. Patients with type I cryoglobulinemia often present with cutaneous findings, such as purpura (Fig 5), acrocyanosis, skin ulcerations or necrosis, or livedo reticularis.¹⁵ Affected individuals may also have a peripheral neuropathy, renal involvement, or arthritis, and the majority of patients also have a severe systemic vasculitis.¹⁶ Renal involvement may be characterized by thrombotic vasculopathy or glomerulonephritis.

Therapy. Treatment for this group of disorders depends on the type and severity of the condition. For patients with type I cryoglobulinemia, the emphasis of treatment is directed towards the underlying lymphoproliferative disorder or the responsible autoimmune disorder. For patients with type II or III cryoglobulinemia, the aim of therapy is directed at the underlying infection, such as hepatitis C, or at the causal autoimmune condition, such as SLE or Sjögren syndrome. Depending on the severity of the illness and organs involved, the same varieties of immune modulating agents are used as discussed previously with regard to the various vasculitic disorders.

Sarcoidosis

Etiology. Sarcoidosis is an acute or chronic systemic granulomatous disease that involves essentially all organ systems, including the skin in 25% of patients. In the United States, the lifetime risk for the development of sarcoidosis is 0.85% for whites and 2.4% for African Americans, favoring middle-aged females. Several genetic associations have been linked to the development of sarcoidosis, but the underlying cause remains unknown. Human leukocyte antigen types, including HLA-DQB1*0201 and HLA-DRB1*0301, are strongly associated with acute disease and a good prognosis, while the butyrophilin-like 2 gene is also associated with sarcoidosis by an unknown mechanism.¹⁷ Granulomatous inflammation in sarcoidosis is characterized by the accumulation of monocytes, macrophages, and activated T-lymphocytes in a T_H1-mediated immune response, leading to increased production of cytokines, including tumor necrosis factor-alpha, interferon-gamma, interleukin-2, and interleukin-12.¹⁸

Clinical manifestations. The cutaneous manifestations of sarcoidosis are highly varied, with numerous morphologic lesion types described. Cutaneous lesions may present as erythematous, violaceous, or brown dermal-based papules, plaques, or nodules with occasional overlying epidermal change, such as scaling or atrophy (Fig 6). Less commonly, verrucous, ulcerative, or ichthyosiform lesions may occur. Rarely, sarcoidosis may present with erythroderma or as hypomelanotic macules and patches. Lesions are usually asymptomatic but may itch in a minority of patients. Common sites of involvement include the face, eyelids, nose, neck, and proximal upper extremities. In general, cutaneous lesions of sarcoidosis do not correlate with the severity or prognosis of systemic involvement, with the exception of erythema nodosum, which is associated with a favorable prognosis.



Fig 6. Sarcoidosis. Erythematous papular noncaseating granulomatous lesions on the shoulder of a patient with sarcoidosis.

Erythema nodosum is the most common nonspecific cutaneous finding in sarcoidosis.^{19,20}

The systemic findings in sarcoidosis are vast. Sarcoidosis may present with fever, polyarthralgias/arthritis, uveitis, hilar adenopathy, or myocarditis. Sarcoidosis may involve the nasal mucosa, upper aerodigestive tract, and parenchyma of the lungs. Granulomatous lesions in bones may occur, and sarcoidosis can involve almost any part of the eye. Other sites of involvement include the lymph nodes, central nervous system, liver, and salivary or lacrimal glands. Renal disease in sarcoidosis occurs occasionally and is usually due to acute interstitial nephritis, nephrocalcinosis, or nephrolithiasis. The rare but classic renal lesion in this disease is a noncaseating, granulomatous interstitial nephritis. In addition, hypercalcemia related to macrophage activity in granulomas at distant sites may also contribute to nephrolithiasis and renal failure.^{19,21}

Therapy. Numerous therapies have been reported as effective in the treatment of cutaneous sarcoidosis. Systemic corticosteroids are consistently beneficial in the treatment of sarcoidal lesions, but long-term utility is often limited by side effects. Intralesional and topical corticosteroids may be effective for limited skin disease. Ultraviolet A light phototherapy has also been reported to be beneficial to some patients. Systemic doxycycline, minocycline, or antimalarial agents may be considered for patients with cutaneous lesions who do not require more aggressive therapy for systemic disease. For patients with more aggressive or systemic disease, immunosuppressive and immunomodulatory treatments may be used. These include methotrexate, leflunomide, thalidomide, cyclophosphamide, azathioprine, mycophenolate mofetil, and tumor necrosis factor-alpha inhibitors.^{19,22}

Systemic sclerosis

Etiology. Systemic sclerosis (SSc), or systemic scleroderma, is an autoimmune connective tissue disorder that is characterized by thickening of dermal collagen bundles with fibrosis and vascular abnormalities affecting the skin and internal organs. Women are 3 times more likely than men to be affected, with peak incidence occurring in the third to fourth decades of life. The pathogenesis of SSc involves vascular endothelial damage via autoimmune mechanisms with subsequent tissue hypoxia, which induces synthesis of profibrotic cytokines, fibroblast activation, and collagen production.²³ Numerous autoantibodies have been shown to contribute to the pathogenesis of SSc, including anticardiolipin, anti-beta₂ glycoprotein I, and antiendothelial cell antibodies. In addition, antitopoisomerase I (Scl-70) antibodies are specific for SSc and contribute to its pathogenesis.²⁴ T lymphocytic infiltrates in SSc have a T_H2-predominant profile, with increased production of profibrotic cytokines, such as interleukin-4 and interleukin-13. More recently, T_H17 lymphocytes and the cytokine interleukin-17 have been implicated as playing a role in SSc. Fibrosis, the final common pathway in SSc lesions, appears to be driven by increased synthesis of collagen, and the complex mechanisms contributing to this pathway have yet to be elucidated.^{23,25}

Clinical manifestations. Raynaud phenomenon of the fingers and toes is the initial manifestation of SSc in the majority of patients. In the early phases of SSc, affected areas are often erythematous and edematous. However, sclerosis of the skin (scleroderma) inevitably ensues and is characterized by tightness, thickening, and nonpitting induration. Cutaneous manifestations of SSc are bilateral, strikingly symmetrical, and include proximal scleroderma (involving the face, neck, trunk, and extremities), sclerodactyly, digital pitting scars of the fingertips, woody acral edema, and abnormal skin pigmentation (often “salt and pepper”). The skin overlying the face, neck, and hands appears stretched, taut, and shiny. Over time, the face may become expressionless, and the hands may appear claw-like. Impaired function of the oral aperture and hands may result. Ventral pterygium may be seen in SSc, and dilated nailfold capillary loops are present in 75% of SSc patients. Matted telangiectases of the face and mucosal surfaces may also occur.^{23,25}

Visceral manifestations include interstitial pulmonary fibrosis, pulmonary arterial hypertension, mid- and lower esophageal dysmotility, intestinal atonia, and myocardial sclerosis. Retinopathy, arthritis with contractual deformities, and osteosclerosis

may also occur. The renal manifestations of SSc are relatively uncommon but can be life-threatening when present. Fortunately, scleroderma renal crisis, a major complication of SSc, occurs in <5% of patients and is characterized by sustained severe hypertension and acute renal failure. Scleroderma renal crisis is believed to be the result of renal vascular injury with a thrombotic microangiopathy, in addition to glomerular and tubulointerstitial sclerosis.^{25,26}

Therapy. Treatment for the cutaneous manifestations of SSc is unsatisfactory. Physical therapy remains a cornerstone for maintaining range of motion of the joints and mouth. Vasodilating drugs, including calcium channel blockers, angiotensin II receptor blockers, prostaglandin analogues, and phosphodiesterase inhibitors are the mainstay of therapy for both Raynaud phenomenon and pulmonary arterial hypertension. Cyclophosphamide and methotrexate may be used for more extensive disease. Phototherapy with ultraviolet A light has been reported for the treatment of cutaneous lesions. Finally, there is good evidence supporting the use of angiotensin-converting enzyme (ACE) inhibitors in managing renal disease in SSc. The role of ACE inhibitors in preventing scleroderma renal crisis remains controversial.^{25,27}

CUTANEOUS MANIFESTATIONS OF CHRONIC KIDNEY DISEASE

Calciphylaxis

Calciphylaxis is an uncommon, severe condition defined by intimal calcification of small- to medium-sized arterioles with subsequent intimal proliferation, thrombosis, and cutaneous necrosis. Calciphylaxis occurs almost exclusively in the setting of ESRD and occurs in ≤4% of patients dependent on dialysis. The risk of calciphylaxis is increased in patients with type 2 diabetes and obese individuals. The vascular calcification in calciphylaxis occurs because of local deposition of calcium in blood vessel walls by vascular smooth muscle cells, which have assumed an osteogenic phenotype, rather than being caused by metastatic calcification.^{28,29}

Clinical manifestations of calciphylaxis begin usually as livedo racemosa, with involved areas of the skin becoming more violaceous, purpuric, and necrotic with advancing disease. Lesions occur most frequently on the lower legs and fatty areas of the body, such as the abdomen, thighs, breasts, and buttocks. Severe pain is a principal feature. Calciphylaxis may result in ischemic myopathy, nonhealing wounds, and sepsis. Overall, calciphylaxis carries a poor prognosis, with 1-year mortality for affected patients exceeding 50%.^{28,29}

Treatment for calciphylaxis is aimed primarily at correcting abnormal calcium metabolism. Specialized dialysis, oral phosphate binders, bisphosphonates, and intravenous sodium thiosulfate have all been reported to have variable success. Sodium thiosulfate holds the most promise among these proposed therapies. Once lesions manifest, surgical debridement or hyperbaric oxygen therapy may be used to improve healing.^{29,30}

Pruritus

Chronic kidney disease (CKD) is the most common systemic cause of pruritus. Pruritus in these individuals is often generalized, intractable, and severe, causing significant morbidity. The mechanism by which renal failure causes pruritus is complex. Contributing factors include xerosis, secondary hyperparathyroidism, increased serum histamine levels, iron deficiency anemia, and neuropathy, all of which have been independently associated with both chronic renal disease and itching.³¹⁻³³

Pruritus in individuals with CKD often responds well to narrowband ultraviolet B light phototherapy. Because many patients with CKD are prone to xerosis, the aggressive use of emollients is advised. Gabapentin and pregabalin, given orally, may also be effective and should be administered after dialysis. Successful treatment of pruritus with topical capsaicin, oral cholestyramine, and thalidomide has also been described in patients with CKD. Finally, renal transplantation provides definitive resolution of pruritus.³¹⁻³³

Acquired perforating dermatosis

Acquired perforating dermatosis has arisen as a term encompassing several entities—perforating folliculitis, Kyrle disease, and acquired perforating collagenosis—that occur in the setting of renal failure or diabetes mellitus. The condition is characterized by numerous dome-shaped papules on the legs, trunk, neck, arms, or scalp with variable degrees of pruritus. The central portion of each lesion often contains a hyperkeratotic core that projects into the dermis, leaving a pit-like depression if removed. Lesions may coalesce to form larger, verrucous plaques. Lesions are believed to be precipitated by trauma, such as scratching or rubbing in response to pruritus. This condition is characterized histologically by the presence of a cup-shaped, epidermal depression into which necrobiotic connective tissue, degenerating inflammatory cells, and collagen bundles are extruded from the dermis.^{34,35}

Treatment with narrowband ultraviolet B light or psoralen plus ultraviolet A light phototherapies may



Fig 7. Photosensitivity secondary to hydrochlorothiazide (HCTZ) use. Well-demarcated erythema on sun-exposed region of the forearm of this patient who was taking HCTZ.

be helpful in managing the pruritus of chronic renal disease, which improves the perforating dermatosis. Aggressive topical emollient use, topical corticosteroids, and topical retinoids may also be beneficial. Other successful therapies reported include allopurinol, doxycycline, isotretinoin, and thalidomide. Renal transplantation usually leads to disease resolution.^{35,36}

Amyloidosis

In patients with ESRD who are receiving dialysis, excess beta-2 microglobulin, which is normally excreted by the kidneys, accumulates in serum and may be deposited as amyloid in certain tissues. The majority of patients who have been undergoing dialysis for ≥ 20 years will develop dialysis-associated amyloidosis, because beta-2 microglobulin is insufficiently filtered through the usual dialysis membranes. This form of amyloid is deposited in synovial membranes, causing musculoskeletal symptoms, such as carpal tunnel syndrome, bone cysts, and spondyloarthropathy. Rarely, subcutaneous nodules may develop in the skin, usually on the buttocks or sacral region. Also, pedunculated papules, lichenoid papules, or localized hyperpigmentation may be seen. Histologically, amyloid protein consisting of beta-2 microglobulin (identified by immunohistochemical stains) is seen in the dermis. The treatment involves high-flux hemodialysis (which has only been shown to delay the progression of dialysis-associated amyloidosis) or renal transplantation.³⁷⁻³⁹

MEDICATION-RELATED NEPHROCUTANEOUS ASSOCIATIONS

In this second section of part II, we discuss medication-related nephrocuteaneous associations, with further division into 3 subsections. In subsections A and B, we focus on dermatologic adverse effects of medications that are frequently prescribed by nephrologists for kidney-related diseases, including hypertension (subsection A)

Table II. Cutaneous side effects of common diuretic agents

Cutaneous side effect	Medication
Hypersensitivity	
Urticaria	Chlorthalidone, furosemide, spironolactone, and indapamide
Purpura	Chlorthalidone, furosemide, and HCTZ
Vasculitis	Chlorthalidone
Photosensitivity	
Morbilliform	Furosemide
Lichenoid	Furosemide, HCTZ, and torsemide
Vesiculobullous	Furosemide and HCTZ
Papulosquamous	HCTZ
Petechial	HCTZ
Lupus-like reaction	Chlorthalidone and HCTZ
Pruritus	Amiloride, furosemide, and HCTZ
Drug-induced cutaneous systemic erythematous	Furosemide, HCTZ, and triamterene
Lichenoid reactions	Furosemide, spironolactone, and triamterene
Exfoliative dermatitis	Furosemide and HCTZ
Jaundice	Amiloride and HCTZ
Alopecia	Amiloride and HCTZ
Morbilliform eruptions	Amiloride and spironolactone
Erythema multiforme/Stevens—Johnson syndrome	Furosemide, HCTZ, and indapamide
Xerostomia	Amiloride
Vesiculobullous eruptions, bullous pemphigoid, and linear immunoglobulin A bullous dermatosis	Furosemide
Eczema	
Pustular lesions (ie, AGEP)	HCTZ
Pseudoporphyria	
Sweet syndrome	
Chronic eczematous reactions	
Erythema annulare centrifugum	
Flushing	
Necrotizing vasculitis	
Hirsutism	Spironolactone

AGEP, Acute generalized exanthematous pustulosis; HCTZ, hydrochlorothiazide.

and renal transplant therapy (subsection B). Antihypertensive medications are among some of the most commonly prescribed therapies. Therefore, even relatively rare dermatologic side effects can impose a significant burden on the population. Some common dermatologic side effects of antihypertensive medications include photosensitivity, morbilliform drug eruptions, and pruritus. Common dermatologic side effects of renal transplant immunosuppressive therapies include increased incidence of cutaneous malignancy and virally mediated sequelae, such as warts and molluscum contagiosum. The third and final subsection (subsection C) will discuss the renal side effects or other renal considerations associated with commonly used dermatologic medications.

Subsection A. Common cutaneous side effects of antihypertensive medications

Diuretics. Common cutaneous side effects of diuretic medications include hypersensitivity,

photosensitivity (Fig 7), pruritus, drug-induced cutaneous SLE, and lichenoid reactions. Notable drug-specific reactions include vesiculobullous eruptions and pustular lesions caused by furosemide and alopecia caused by amiloride and hydrochlorothiazide. Table II provides a comprehensive list of cutaneous side effects of common diuretic agents.⁴⁰⁻⁹⁵

Angiotensin-converting enzyme inhibitors. The overall incidence of adverse reactions to ACE inhibitors is estimated at 28%, half of which are cutaneous in nature.⁹⁶ These cutaneous reactions include angioedema (most commonly seen with lisinopril use),⁹⁷ pruritus, vesiculobullous eruptions (Fig 8), urticaria, other generalized eczematous eruptions, photosensitivity, and hair loss.⁹⁶ ACE inhibitor-induced angioedema is quite rare, occurring in only 0.1% to 0.2% of patients, but is the most feared consequence given its potentially life-threatening nature.⁹⁸ Additional side effects are summarized in Table III.^{61,92-126}



Fig 8. Bullous pemphigoid caused by captopril use. Bullous eruption in a patient taking captopril.

Angiotensin II receptor-blocking drugs.

Losartan has been reported to cause nonspecific eczematous eruptions, alopecia, xerosis, dermatitis, ecchymosis, erythema, flushing, angioedema, photosensitivity, pruritus, hyperhidrosis, and urticaria.^{127,128} Cases have been reported of losartan-induced superficial peeling of the palms with hemolysis,¹²⁹ Henoch–Schönlein purpura,¹³⁰ and cutaneous T-cell pseudolymphoma.¹³¹

Adrenergic agents. *Beta-blockers.* Beta-blockers are another mainstay of antihypertensive therapy. Cutaneous side effects of beta-blockers include Raynaud phenomenon, photosensitivity, dry eyes, thrombocytopenic purpura, reversible alopecia, lichenoid, eczematous, and psoriasiform eruptions.^{132–134} Beta-blockers have also been reported to induce or worsen psoriasis.¹³⁵ Case reports exist detailing beta-blocker-induced vasculitis,^{136,137} subacute cutaneous lupus erythematosus,¹³⁸ and fixed drug eruption¹³⁹ (Fig 9). Among beta-blockers, acebutolol has the highest propensity for inducing antinuclear antibody formation.¹⁴⁰

Alpha-blockers. Cutaneous side effects of alpha-blocking agents include pruritus, increased sweating, eczematous eruptions, and macular or morbilliform eruptions.^{92,94,127} Patients may also develop a positive antinuclear antibody serology with prazosin.¹²⁹

Calcium channel blockers. Overall, adverse cutaneous reactions associated with calcium channel blockers are uncommon, with an incidence of 1%.¹⁴¹ Cutaneous and mucosal side effects include gingival hyperplasia (diltiazem [21%] > verapamil [19%] > nifedipine [<10%]), facial and truncal telangiectasia, new onset or exacerbation of psoriasis, photosensitivity reactions, SCLE, gynecomastia, acute generalized exanthematous pustulosis (AGEP) (Fig 10), erythromelalgia, and oral ulcers.^{142–153} Table IV outlines common side effects and causative agents.^{92,97,154–204}

Table III. Cutaneous side effects of angiotensin-converting enzyme inhibitors

Cutaneous side effect	Medication
Angioedema	Lisinopril, captopril, enalapril, and fosinopril
Photosensitivity	Captopril, fosinopril, lisinopril, and ramipril
Pruritus	Captopril, fosinopril, and ramipril
Urticaria	Enalapril, fosinopril, and ramipril
Alopecia	Enalapril, lisinopril, and ramipril
Bullous eruptions	Captopril, enalapril, and ramipril
Drug-induced pemphigus	
Bullous pemphigoid	Captopril and enalapril
Morbilliform eruption	Captopril and enalapril
Henoch–Schönlein purpura	
Lichenoid eruptions	
Psoriasis	Enalapril and lisinopril
Erythema multiforme	Enalapril and ramipril
Eczematous eruptions	Fosinopril and lisinopril
Hyperhidrosis	Fosinopril and ramipril
Pityriasis rosea–like eruption	Captopril
Oral aphthae	
Exfoliative dermatitis	
Vasculitis	Enalapril
Gynecomastia	
Flushing	Lisinopril
Purpura	Ramipril

Direct vasodilators. Common side effects of vasodilatory antihypertensive agents include pruritus, urticarial, eczematous eruptions, flushing, photosensitivity, and angioedema. Notable specific reactions include Sweet syndrome from hydralazine (Fig 11), darkening of cartilage and black tongue from methyldopa, and hypertrichosis from minoxidil. These effects are summarized in Table V.^{92,93,95,107,129,146,205–237}

Subsection B. Cutaneous considerations in renal transplant patients

The chronic use of immunosuppressive agents to prevent renal allograft rejection increases the risk of cutaneous sequelae in renal transplant patients compared to the general population. This subsection will discuss cutaneous considerations in this group of patients.

Skin cancers. The chronic use of immunosuppressive medications to prevent allograft rejection increases the long-term risk of malignancy in renal transplant patients compared with the general population. It is recommended that renal transplant



Fig 9. Fixed drug eruption secondary to beta-blocker use. Erythematous lichenoid drug eruption on the shin of a patient taking atenolol.



Fig 10. Acute generalized exanthematous pustulosis caused by diltiazem use. Note the evenly distributed pinpoint pustules on the trunk of a patient taking diltiazem.

patients undergo monthly self-skin examinations and every 6-month to yearly total body skin examinations performed by a dermatologist.²³⁸

Nonmelanoma skin cancer. Skin is the most common site for the development of malignancy in renal transplant patients, particularly cutaneous squamous cell carcinomas (SCCs) and basal cell carcinomas (BCCs),²³⁹ which account for >90% of all skin cancers in transplant recipients.²⁴⁰ The incidence of cutaneous carcinomas increases with duration and dosage of immunosuppressive therapy, with two Australian studies estimating the incidence increasing from approximately 7% after 1 year of therapy²⁴¹ to 82% after 20 years.²⁴² Other risk factors include fair skin,²⁴³ significant ultraviolet radiation exposure,²⁴⁴ and pretransplant history of SCC, BCC, or actinic keratoses (AKs).²⁴⁴

SCC is the most common skin cancer in renal transplant recipients, occurring 65 to 250 times as frequently as in the general population.²⁴⁵ The risk of SCC appears to increase exponentially, as contrasted with a linear increase in risk of BCC.²⁴⁶ BCC incidence increases by a factor of 10 to 16 in renal transplant patients.^{247,248} The mean interval between

Table IV. Cutaneous side effects of calcium channel blocking antihypertensive agents

Cutaneous side effect	Medication
Pruritus	Amlodipine, diltiazem, nicardipine, nifedipine, and verapamil
Morbilliform eruption	Amlodipine, diltiazem, nifedipine, and verapamil
Gingival hyperplasia	Amlodipine, diltiazem, and verapamil
SJS/TEN	Amlodipine, diltiazem, and verapamil
Purpura	Amlodipine and nifedipine
Subacute cutaneous lupus	
Erythema multiforme	Amlodipine and verapamil
Gynecomastia	
Acute generalized exanthematous pustulosis	Diltiazem and nifedipine
Photosensitivity	
Angioedema	
Flushing	Diltiazem and verapamil
Increased sweating	
Vasculitis	
Urticaria	Nifedipine and verapamil
Alopecia	Verapamil
Hypertrichosis	

SJS/TEN, Stevens-Johnson syndrome/toxic epidermal necrolysis.

transplantation and diagnosis of a cutaneous carcinoma is 8 years for patients who received transplants at 40 years of age,²⁴⁹ but only 3 years for those receiving transplants after 60 years of age.²⁴⁶ Most organ transplant recipients with a first SCC will subsequently develop multiple NMSC within 5 years.²⁴⁰ Furthermore, SCCs behave more aggressively in transplant recipients than in non-immunosuppressed persons.²⁵⁰

Prevention and screening. It is recommended that renal transplant recipients receive aggressive preventative therapy, including primary prevention through minimizing ultraviolet light exposure and secondary prevention via close follow-up with a dermatologist. For low-risk individuals with no history of skin cancer, dermatologic follow-up can be yearly; for higher-risk patients (ie, those with fair skin, a history of sunburns, or older age), follow-up should occur at 6- to 12-month intervals. For the highest risk individuals with a history of NMSCs or precursor lesions, follow-up should be every 3 months.²⁵¹ Secondary prevention can also include the use of topical retinoids to treat AKs and diminish recurrence rates of SCCs. In addition, long-term use of systemic retinoids, such as low-dose acitretin, could be recommended for transplant recipients with multiple and/or recurrent skin cancers.^{238,248,252-256} Studies have shown that the current



Fig 11. Sweet syndrome caused by hydralazine use. Erythematous, indurated plaques on the throat of a patient taking hydralazine.

level of dermatologic surveillance in this patient population is likely inadequate and recommend the integration of dermatologists into the transplant team.^{257,258}

Melanoma. The largest published investigation to date found that renal transplant recipients are 3.6 times more likely to develop melanoma than the general population.²⁵⁹ However, the mechanism for this observation is uncertain.²⁶⁰ Risk factors include increasing age, high personal sun exposure, large numbers of nevi, intensity and duration of immunosuppression, and receipt of lymphocyte-depleting antibody.^{260,261} Risk is inversely associated with female sex and nonwhite race.²⁶⁰ The mean interval between transplantation and the diagnosis of melanoma is 5 years.²⁶²

Kaposi sarcoma. Kaposi sarcoma (KS) is a tumor of endothelial origin that is associated with human herpesvirus-8 (HHV-8; Fig 12). It occurs more frequently in the setting of immunosuppression.²³⁹ In transplant recipients, KS occurs in certain ethnic groups linked to the geographic distribution of HHV-8, including those of Mediterranean, Jewish, Arabic, Caribbean, or African descent.²⁶³ In a South African cohort study, KS was the most common cancer detected in nonwhite renal transplant recipients.²⁶³ In contrast to NMSC and melanoma, KS usually appears early after transplantation. The mean interval from transplantation to KS diagnosis is 13 months.²⁴³ KS in transplant patients has a male:female ratio of 3.3:1.0.²⁴³ Approximately 90% of patients develop cutaneous or mucosal lesions, and visceral involvement develops in 25% to 30% of renal transplant patients.²⁴³

Merkel cell carcinoma. Merkel cell carcinoma (MCC) is a rare neuroendocrine tumor that usually presents as a red or red-blue papule or nodule in a sun-exposed area (Fig 13). One review found the general organ transplant population to have an increased risk of MCC of 6:1 compared to 65:1 in the general population.²⁶⁴ MCC occurs

predominantly in male transplant recipients, and the mean age at time of diagnosis is younger than in the general population.²⁴³ MCC develops an average of 7.5 years after transplantation, usually occurring on the head, neck, or arms.²⁴³

Human papillomavirus-associated lesions.

Immunosuppression can reactivate the human papillomavirus (HPV), likely because of reduced immune surveillance.²⁶⁵ Malignancies associated with HPV, including cervical, anal, vulvar, vaginal, and penile cancers and precancerous lesions, such as cervical intraepithelial neoplasia (CIN), are significantly increased after renal transplantation.²⁶⁶⁻²⁷² One review reported an increased standardized incidence ratio (SIR) of HPV-associated cancers in transplant patients compared to the general population, including cervical (SIR, 2.1), vulvar/vaginal (SIR, 22.8), penile (SIR, 15.7), and anal (SIR, 4.9) malignancies.²⁷³ In addition to malignancies, HPV can cause other conditions, such as anogenital and mucocutaneous warts (Fig 14). The prevalence of cutaneous warts in transplant recipients is proportional to the duration of immunosuppression, increasing to 50% to 90% in patients who are >4 to 5 years posttransplantation.²⁶⁵ This association underscores the necessity of Papanicolaou smears and genitourinary examinations, possibly including anal Papanicolaou tests, in addition to routine skin examinations in renal transplant patients. The United States Preventive Task Force recommends that women receive Papanicolaou tests every 6 months for the first year after transplantation. If these tests are normal, annual screening is adequate.²⁶⁵

Molluscum contagiosum. Molluscum is a poxvirus that causes flesh-colored, dome-shaped papules. It is associated with immunodeficient states, including HIV infection, inherited immunodeficiency, or after treatment with immunosuppressive drugs following renal transplantation. Immunocompromised patients can develop severe, persistent cases of molluscum. There also exists a case report of a renal transplant patient developing multiple giant molluscum lesions.²⁷⁴ Though molluscum is a known complication seen in organ transplant recipients, it occurs more frequently in heart and lung transplant recipients²⁷⁵ than in renal transplant recipients. One study assessing skin disease in 200 children who received organ transplants (mostly renal allografts) found the prevalence of molluscum to be 6.9%,²⁶¹ within the 5.1% to 11.5% estimated point prevalence of MC in the general pediatric population.²⁷⁶

Drug eruptions. Any patient with an inborn, acquired, or iatrogenic immunodeficiency is prone

Table V. Cutaneous side effects of common antihypertensive vasodilatory agents

Cutaneous side effect	Medication
Pruritus	Clonidine, isosorbide mononitrate, methyldopa, pentoxifylline, and sildenafil citrate
Urticaria	Cilostazol, hydralazine, methyldopa, pentoxifylline, and sildenafil citrate
Eczematous eruptions	Hydralazine, isosorbide mononitrate, methyldopa, and pentoxifylline
Flushing	Hydralazine, nitroglycerine, pentoxifylline, and sildenafil citrate
Photosensitivity	Hydralazine, methyldopa, and sildenafil citrate
Angioedema	Clonidine, hydralazine, and pentoxifylline
Drug-induced lupus	Hydralazine (10% of pts) and methyldopa
Exfoliative dermatitis	Hydralazine and sildenafil citrate
SJS/TEN	Hydralazine and minoxidil
Xerosis	Cilostazol
Furunculosis	
Cicatricial pemphigoid	Clonidine
Pityriasis rosea—like drug eruption	Hydralazine
Sweet syndrome	
Livedo reticularis	
Fixed drug eruption	
Hyperpigmentation	Methyldopa
Lichen planus	
Erythema multiforme	
Darkening of cartilage	
Black tongue	
Gynecomastia	
Hypertrichosis	Minoxidil

SJS/TEN, Stevens—Johnson syndrome/toxic epidermal necrolysis.

to developing drug-induced exanthems, consisting of morbilliform, macular, or papular eruptions.²⁷⁷

Sirolimus-based therapy adverse effects. Many renal transplant patients receive sirolimus-based immunosuppressive therapy. A 2005 study of 80 renal transplant patients receiving sirolimus-based therapy found that 99% experienced cutaneous adverse events. The most frequent were of pilosebaceous apparatus involvement, including acne-like eruptions (46%), scalp folliculitis (26%), and hidradenitis suppurativa (12%). Edematous complaints included chronic edema (55%) and angioedema (15%). Mucous membrane disorders included aphthous ulcerations (60%), epistaxis (60%), chronic gingivitis (20%), and chronic fissuring of the lips (11%). Finally, nail disorders included chronic onychopathy (74%) and periungual infections (16%).²⁷⁸ A 2013 study of 50 patients had similar findings, reporting skin infections (78%), facial hyperpigmentation (50%), and acneiform eruption (46%).²⁷⁹

Subsection C. Renal side effects and considerations of dermatologic medications

Many systemic medications commonly used by dermatologists to treat cutaneous disease also have significant renal effects or require special consideration of renal function for initial or subsequent

dosing. This third subsection will focus on dermatologic medications with adverse renal effects or other special renal considerations.

Cyclosporine. Cyclosporine is a potent immunosuppressive agent that is approved by the US Food and Drug Administration for the treatment of psoriasis and is commonly used off-label for severe atopic dermatitis²⁸⁰ and pyoderma gangrenosum.^{281,282} One of cyclosporine's adverse effects is nephrotoxicity,^{283,284} which may occur acutely through afferent arteriolar vasoconstriction^{285,286} or chronically.²⁸⁷ Acute renal toxicity is dose-dependent and reversible.^{288,289} Cyclosporine is primarily metabolized by hepatic and intestinal CYP3A4, which can be inhibited by triazole antifungal agents and erythromycin.^{290,291} Concurrent use of these medications with cyclosporine can increase the risk of nephrotoxicity, neurotoxicity, and elevated blood pressure. In contrast, trimethoprim-sulfamethoxazole (TMP-SMX) can reduce serum cyclosporine levels. Concomitant use of cyclosporine with TMP-SMX can lead to reversible nephrotoxicity in renal transplant recipients, increasing serum creatinine levels and potentially predisposing patients to organ rejection.^{292,293}

Methotrexate. Methotrexate (MTX) competitively inhibits the enzyme dihydrofolate reductase,



Fig 12. Kaposi sarcoma. Violaceous papules on the back of an immunosuppressed renal transplant recipient.



Fig 13. Merkel cell carcinoma.

leading to decreased DNA and RNA synthesis and ultimately inhibition of cell division. It is approved by the US Food and Drug Administration for use by patients with cutaneous lymphomas and psoriasis, psoriatic arthritis, and rheumatoid arthritis (RA).²⁹⁴⁻²⁹⁷ However, it is widely used for many other dermatologic conditions, including autoimmune connective tissue diseases,²⁹⁸⁻³⁰⁶ immunobullous dermatoses,³⁰⁷⁻³¹⁰ proliferative disorders such as pityriasis lichenoides et varioliformis acuta



Fig 14. Human papillomavirus-associated lesions. Note the hypopigmented papules in the oral cavity of an immunosuppressed patient.

(PLEVA),³¹¹ systemic vasculitis,³¹² and sarcoidosis.³¹³⁻³¹⁵

MTX is excreted predominantly through the kidney. Therefore, drugs that decrease glomerular filtration or active tubular secretion (eg, salicylates, nonsteroidal antiinflammatory drugs, and sulfonamides) can increase the plasma concentration of MTX.^{316,317} This may lead to greater drug potency and increased toxicity. Primary renal toxicity from MTX occurs with high-dose therapy (50-250 mg/m² intravenously), generally used only in chemotherapy regimens for malignancy treatment. Such high doses can lead to MTX precipitation in the renal tubules and induce crystal nephropathy.³¹⁸⁻³²⁰ It is important to check renal function (ie, blood urea nitrogen and serum creatinine) before MTX initiation and as routine monitoring at least once or twice yearly,³¹⁴ regardless of the disease indication or MTX dose.

Rituximab. Rituximab, a monoclonal antibody directed against the B-cell surface antigen CD20, is approved by the US Food and Drug Administration for the treatment of non-Hodgkin lymphoma, chronic lymphocytic leukemia, and refractory rheumatoid arthritis.^{321,322} It is also used off-label in dermatology to treat various autoimmune connective tissue diseases, such as dermatomyositis and cutaneous SLE, immunobullous dermatoses, graft versus host disease, vasculitis, and cutaneous B-cell lymphoma.³²³⁻³³⁹ Adverse events reported with rituximab therapy include tumor lysis syndrome in patients being treated for malignancy (<0.05%) who are unable to adequately clear killed tumor cell debris. This adverse event usually occurs within 12 to 24 hours of rituximab infusion and is characterized by a rapid decline in renal function.³⁴⁰

Sulfonamides. The most commonly used sulfonamide, TMP-SMX, is used in dermatology as a second-line agent for acne vulgaris and as an often first-line agent for uncomplicated skin and soft tissue infections caused by community-acquired methicillin-resistant *Staphylococcus aureus*

(CA-MRSA).³⁴¹⁻³⁴⁴ Renal adverse events to be aware of in patients taking TMP-SMX include intrinsic renal impairment, interstitial nephritis, and hyperkalemia.³⁴⁵⁻³⁴⁸ In addition, because approximately 30% to 60% of TMP and 20% to 40% of SMX is excreted via the kidneys, dose adjustments must be made for patients with renal insufficiency.^{292,349}

Tetracyclines. Tetracycline antibiotics are prevalent dermatologic drugs owing to their application in the treatment of two of the most common dermatologic conditions, acne and rosacea. These antibiotics are also used for other chronic inflammatory facial dermatoses, including perioral dermatitis.³⁵⁰⁻³⁵⁶ Tetracyclines may also be used to treat immunobullous dermatoses, granulomatous dermatoses, superficial CA-MRSA infections, Rickettsial diseases, and spirochete infections.^{343,351-353,357-368} This drug class is primarily known to cause gastrointestinal adverse events, but tetracycline antibiotics can also affect the kidneys. Hypersensitivity reactions, most commonly with minocycline, can uncommonly affect the kidneys in the form of nephritis^{369,370} as part of the drug-induced hypersensitivity syndrome (DIHS), or drug reaction with eosinophilia and systemic symptoms (DRESS). Notably, renal failure prolongs the half-life of most tetracycline antibiotics, with the exception of doxycycline, which is cleared predominantly by the gastrointestinal tract and is appropriate for patients with renal failure.^{371,372}

Spironolactone. In dermatology, spironolactone is primarily used for its antiandrogenic effects in females to treat conditions such as polycystic ovarian syndrome (PCOS), hirsutism, androgenetic alopecia, acne vulgaris, and hidradenitis suppurativa.³⁷³⁻³⁸⁷ Given that spironolactone is also an aldosterone antagonist, its most common adverse effect is hyperkalemia.³⁸⁸ Spironolactone is, therefore, not recommended in patients with renal insufficiency or in those taking concomitant medications that may also increase potassium levels, such as ACE inhibitors, angiotensin II receptor blockers, or other aldosterone inhibitors.³⁸⁸⁻³⁹² It may be prudent to obtain a complete blood count and chemistry profile to rule out preexisting renal dysfunction or hyperkalemia before starting a patient on spironolactone. As needed, monitoring can then continue every 4 to 6 weeks and/or with every dosage increase, until serum potassium level stabilization occurs. Blood pressure and weight should also be periodically monitored.³⁹²⁻³⁹⁴ Also, spironolactone can rarely cause agranulocytosis, the likelihood of which is increased with renal impairment.³⁹⁵

Allopurinol. Allopurinol is traditionally used to treat tophaceous gout and/or hyperuricemia, but

has also been used off-label in dermatology for rare cutaneous diseases, such as perforating dermatoses.^{396,397} Though its adverse effect of Stevens-Johnson syndrome/toxic epidermal necrolysis is perhaps most notorious among dermatologists, allopurinol can also cause DIHS (or DRESS). Interstitial nephritis is one of many diagnostic components of DIHS/DRESS.³⁹⁸⁻⁴⁰⁰ In a review of 60 patients with DIHS, allopurinol was the culprit drug in 32% of cases.⁴⁰¹ Chronic renal impairment was also observed as a common clinical feature of allopurinol-induced DIHS/DRESS.⁴⁰¹ Finally, allopurinol may also cause interstitial nephritis independent of DIHS/DRESS.⁴⁰²

In conclusion, dermatologists need to remain aware of inflammatory dermatoses associated with renal abnormalities and know when nephrologist referral is warranted for work-up and management of potential renal complications. It is also imperative to recognize cutaneous side effects of renal medications as well as remain cognizant of how many common dermatologic medications may impact kidney function or may need dose adjustment in patients with renal insufficiency.

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Hereditary melanoma: Update on syndromes and management

Genetics of familial atypical multiple mole melanoma syndrome

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Learning objectives

After completing this learning activity, participants should be able to describe algorithms used to assess patients with possible familial atypical mole melanoma syndrome (FAMM); explain the genetic basis of FAMM predisposition, in light of novel susceptibility genes identified recently in genomic studies; discuss the current role of genetic counseling in patients with FAMM and their relatives; and determine when patient referral to other specialists for FAMM is appropriate.

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Malignant melanoma is considered the most lethal skin cancer if it is not detected and treated during its early stages. About 10% of melanoma patients report a family history of melanoma; however, individuals with features of true hereditary melanoma (ie, unilateral lineage, multigenerational, multiple primary lesions, and early onset of disease) are in fact quite rare. Although many new loci have been implicated in hereditary melanoma, *CDKN2A* mutations remain the most common. Familial melanoma in the presence of multiple atypical nevi should raise suspicion for a germline *CDKN2A* mutation. These patients have a high risk of developing multiple primary melanomas and internal organ malignancies, especially pancreatic cancer; therefore, a multidisciplinary approach is necessary in many cases. The value of dermoscopic examination and total body photography performed at regular intervals has been suggested by a number of studies, and should therefore be considered for these patients and their first-degree relatives. In addition, genetic counseling with the possibility of testing can be a valuable adjunct for familial melanoma patients. This must be performed with care, however, and only by qualified individuals trained in cancer risk analysis. (J Am Acad Dermatol 2016;74:395-407.)

Key words: *CDK4; CDKN2A; familial melanoma syndromes; FAMMM; melanoma genetics; mixed cancer syndromes.*

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GENERAL CONSIDERATIONS FOR HEREDITARY MELANOMA

Key point

- Hereditary melanomas can appear as part of a familial melanoma syndrome or a mixed cancer syndrome

Cutaneous malignant melanoma (CMM) can be highly lethal if it is not detected and treated during its early stages. The incidence of melanoma has increased in the past several decades. In developed countries, CMM is the sixth most common cancer, accounting for >47,000 deaths worldwide annually (45% occurring in Europe). The rise in incidence affects both young and older populations, while the global projected incidence of melanoma for the year 2025 is estimated to be 317,000 new cases compared to the 200,000 cases reported in 2008.¹

About 7% to 15% of melanoma cases occur in patients with a family history of melanoma; however, this does not necessarily indicate that a single genetic mutation is being transmitted in those kindreds.² Most cases of familial melanoma are caused by shared sun exposure experiences among family members with susceptible skin types.² In aggregate, about 45% of familial melanomas are actually associated with germline mutations in *CDKN2A* or *CDK4*. There does not appear to be another major locus beyond *CDKN2A*, because the prevalence of the new melanoma predisposition genes are quite rare (see part II of this continuing medical education article). Although great strides have been made in identifying other novel cosegregating variants within melanoma kindreds, it is likely that many rare disease-causing mutations remain undiscovered.³ The term mixed cancer syndrome (MCS) can be applied to familial conditions for which there is a high incidence of various cancers in general, including melanoma. In the past few years, melanomas have also been found to arise in families that are generally prone to specific patterns of malignancies. The term melanoma tumor syndrome might be more appropriate to discriminate it from hereditary melanoma, where the dominant cancer phenotype is that of CMM.

FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA (OMIM 155601) AND FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA–PANCREATIC CANCER (OMIM 606719) SYNDROMES

Key point

- A positive association between melanoma, multiple nevi, pancreatic cancer, and *CDKN2A* mutations is now well established

The first documented case of familial melanoma was reported by Norris⁴ in 1820; his patient was a 59-year-old man with melanoma, a high total body nevus count, and a family history of melanoma. More than a century after Norris made his observations, Lynch and Krush⁵ described familial atypical multiple mole melanoma (FAMMM) syndrome, which comprised an association between pancreatic cancer (PC), multiple nevi, and melanoma. Contemporaneously, Clark described a similar phenotype, B-K mole syndrome, consisting of familial melanoma in the setting of numerous atypical nevi.⁶ In the early 1990s, several groups reported germline mutations in the cell cycle gene *p16* (now *CDKN2A*) among a subset of FAMMM kindreds.^{7,8}

CLINICAL FEATURES OF FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Key points

- Patients suspected to have FAMMM present with multiple atypical nevi (>50) and have a positive personal or family history of melanoma
- Patients with FAMMM present with melanomas at a younger age and are at a higher risk to develop a second primary melanoma compared to the general population
- Patients with FAMMM may also develop cutaneous melanomas on normal skin in spite of the large number of atypical nevi at presentation

FAMMM is a clinical phenotype comprised of numerous nevi (Fig 1, A), some atypical, and a family history of melanoma; some diagnostic elements of the FAMMM phenotype are outlined in Table I. Documenting a thorough family history of cancer, particularly melanoma, is of utmost importance because it is a critical element of FAMMM syndrome. Particular attention should be paid to the age at which CMM and other cancers (Table II) have been diagnosed in family members—as well as family skin phototype (ie, red hair and fair skin)—because these traits may be associated with higher disease risk.⁹ In patients suspected of having FAMMM, careful examination of all nevi should be performed not only on the patient of interest but also their first- and second-degree relatives.

Nevi in patients with FAMMM are phenotypically diverse (Fig 1, A). It is not unusual to observe multiple nevi with marked atypia, some bearing a striking resemblance to melanoma, interspersed between numerous benign-looking nevi. Atypical nevi



Fig 1. The familial atypical multiple mole melanoma (FAMMM) phenotype. **A**, Clinically atypical moles frequently associated with FAMMM syndrome. **B**, Pedigree of a FAMMM kindred showing multiple early onset cutaneous melanomas (proband and brother) and pancreatic cancer (PANC CA; mother). The patient and mother are carriers of a p16 mutation (m). **C**, Patients with FAMMM syndrome (in particular those with germline *CDKN2A* mutations) are at risk for cutaneous melanoma, pancreatic cancer, and neural systems tumors (melanoma-astrocytoma syndrome). *DN*, Dysplastic nevi; *MEL*, cutaneous melanoma; *PANC CA*, pancreatic cancer; *PR CA*, prostate cancer.

are more likely to undergo malignant transformation when compared to banal nevi; melanomas in patients with FAMMM, however, often develop on normal skin.^{10,11}

While it is clear that patients with FAMMM syndrome have a dramatically increased risk of melanoma, it is less clear whether there are inherent differences between FAMMM-associated and sporadic melanomas. Patients with FAMMM seem to be more prone to developing superficial spreading and nodular melanomas,¹² which is interesting in light of other findings suggesting that *CDKN2A*-mutant CMMs are significantly less invasive (ie, with lower Clark levels) than *CDKN2A*-wild type CMMs.¹³ No statistically significant differences in location and Breslow thickness have been

reported between sporadic melanoma controls and patients with FAMMM. Sargent et al¹⁴ have recently reported that *CDKN2A* mutation-positive CMMs tend to have histologic features that are compatible with superficial spreading melanomas, including higher pigmentation (*P* for trend = .02), increased pagetoid scatter (*P* for trend = .07), and a non-spindle cell morphology in the vertical growth phase. However, more information is required to establish specific histopathologic features indicative of a CMM from a *CDKN2A* mutation-positive patient. Gillgren et al¹⁵ found that familial melanomas have a tendency to occur on the trunk more so than on the head and neck. Recent studies have shown similar rates of somatic *BRAF* and *NRAS* mutations in patients with or without germline

Table I. Criteria for the diagnosis of familial atypical multiple mole melanoma*

1. Cutaneous melanoma in ≥ 1 first- or second-degree relatives
2. High total body nevi count (>50) and multiple atypical nevi
3. Specific histologic features present in nevi, including: asymmetry, subepidermal fibroplasia, lentiginous melanocytic hyperplasia with spindle or epithelioid melanocytes, variable dermal lymphocyte infiltration, and the presence of "shouldering" phenomenon

*All criteria must be present to make a diagnosis.⁵⁸

CDKN2A mutations. Zebary et al¹⁶ reported that *BRAF* and *NRAS* mutations occurred in 43% and 11% of CMMs, respectively, in *CDKN2A* mutation carriers, compared to 39% and 14% of CMMs in non-*CDKN2A* mutation controls; similar findings were echoed by others.¹⁷ The pattern of metastasis between patients with familial and sporadic melanoma does not appear to differ, so a distinct postmelanoma follow-up program is probably not necessary for patients with FAMMM.¹⁸ However, as will be discussed below, the risk of PC among some patients with FAMMM does warrant special consideration.

An example of a typical FAMMM pedigree is shown in Fig 1, B. The proband presented with multiple atypical nevi (>200) and has had >10 histologically confirmed CMMs. Her mother developed PC at 63 years of age and died. Genetic testing revealed a single base pair deletion (c.132delC) that was shared by both the proband and the mother. The key elements of FAMMM are embodied in this pedigree: early age of onset (22 years of age), multiplicity of CMMs ($n = 12$), a family history of melanoma, dysplastic nevi, PC, and a documented deleterious cosegregating mutation on one side of the family.

THE GENETICS OF FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME

Key points

- The *CDKN2A* locus is the major recurrent source of germline mutagenesis in hereditary melanoma
- The prevalence of germline *CDKN2A* mutations in families with melanoma and *CDKN2A* mutation penetrance vary with geographic location
- Patients that harbor the mutation have a higher risk of developing melanoma; however, some evidence suggests that these CMMs may be less invasive than *CDKN2A*-wild type CMMs

Table II. Malignancies (besides melanoma) reported with *CDKN2A* and *CDK4* mutations^{3,20,21,38,59-61,69-71}

<i>CDKN2A</i> mutations	<i>CDK4</i> mutations
Uveal melanoma	—
Breast cancer	Breast cancer (Phyllodes tumor)
Ovarian tumors	Ovarian tumors
Cervical cancer	Cervical cancer
Endometrial cancer	—
Pancreatic cancer	Pancreatic cancer
Stomach cancer	Stomach cancer
Esophageal cancer	—
Colon cancer	Colon cancer
Lung cancer	Lung cancer
Leukemia	—
Lymphoma (Hodgkin)	Lymphoma
Brain/central nervous system tumors	—
Renal cell carcinoma	—
Urinary bladder carcinoma	—
Prostate cancer	Prostate cancer
Hepatic cancer	—
Sarcomas	—
Parotid gland tumors	—
Tonsillar tumors	—
Nasopharyngeal/laryngeal tumors	—
Tongue cancer	—

The dominant molecular pathway involved in FAMMM is shown in Fig 2. *CDKN2A* is located on chromosome 9p21.3, and its alterations are most commonly associated with FAMMM syndrome. Typically, germline mutations of *CDKN2A* seen in CMM and PC-prone kindreds are missense or nonsense mutations that impair the inhibitory functions of p16 and/or p14ARF. *CDKN2A* is comprised of 4 exons (1 α , 1 β , 2, and 3) that are used to encode for 2 proteins: p16 (1 α , 2, and 3) and p14ARF (exons 1 β , 2, and 3). p16 inhibits cyclin-dependent kinase 4 (CDK4) and CDK6, thereby preventing the phosphorylation of retinoblastoma protein (RB1). A hypophosphorylated RB1 molecule sequesters and prevents the transcription factor E2F1 from inducing S phase genes and triggering G₁ to S transition. On the other hand, p14ARF antagonizes HDM2, which ubiquitinates the tumor suppressor p53, thereby condemning p53 for proteasomal degradation.¹⁹ Accelerated destruction of p53 abolishes the normal DNA damage and G₂ checkpoint responses.¹⁹ Therefore, inactivation of the *CDKN2A* locus enhances proliferation and reduces apoptosis. The prevalence of germline *CDKN2A* mutations has been found to vary with

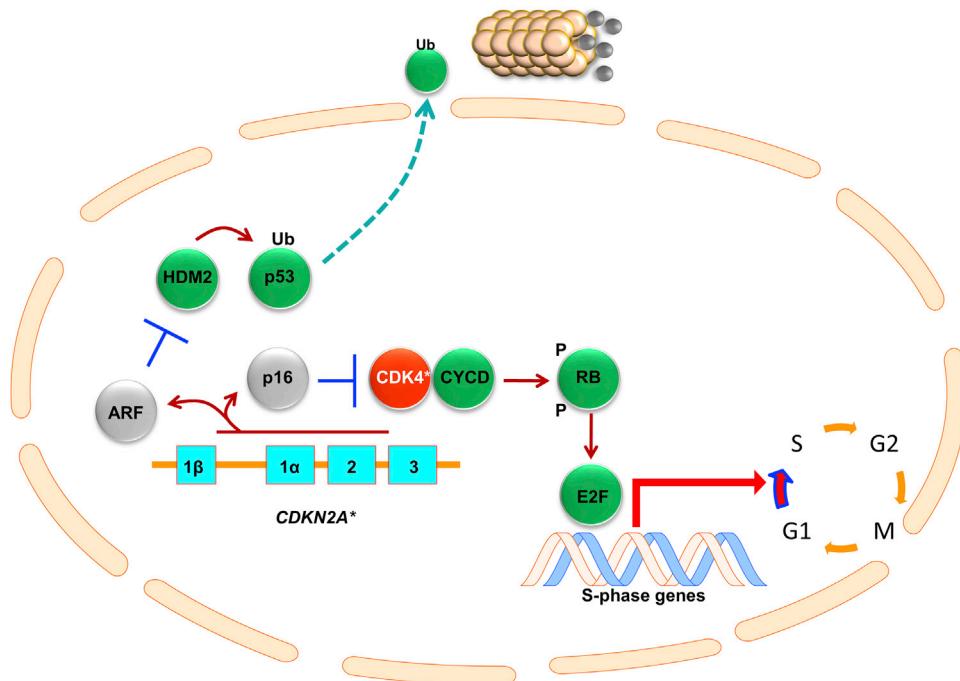


Fig 2. Pathways linked to familial atypical multiple mole melanoma (FAMMM) predisposition. *CDKN2A* is comprised of 4 exons (ie, 1 α , 1 β , 2, and 3). Exons 1 α , 2, and 3 encode for p16; exons 1 β , 2, and 3 encode for p14ARF (ARF). p16 inhibits CDK4, which, without p16, binds cyclin D (CYCD) and phosphorylates (P) the retinoblastoma protein (RB). This in turn releases E2F transcription factors, which induces G₁ phase genes and triggers G₁ to S cell cycle transition. p14ARF inhibits HDM2, which normally ubiquitinates (Ub) p53, condemning it to destruction by the proteasome. Mutations in *CDKN2A* (*CDKN2A**) leads to the loss of p14ARF and p16 function (gray) while mutations in *CDK4* (*CDK4**) renders CDK4 resistant to p16 inhibition, thereby activating CDK4 activity (red); nonmutated genes are shown in green.

geography and the family context.^{3,20,21} In a metaanalysis by Goldstein et al,²² 39% of families (with ≥ 3 affected family members) had germline *CDKN2A* mutations, ranging from 20% (32/162) in Australia to 45% (29/65) in North America to 57% (89/157) in Europe. Similarly, in a study of Greek families, Nikolaou et al²³ reported that 22% of familial melanoma cases and 57% of individuals with multiple primary melanomas carried a *CDKN2A* mutation. When melanoma cases were ascertained independent of family history, there was a much lower rate of mutation. The frequency of *CDKN2A* mutations in patients with a single primary melanoma or multiple primary melanomas were 1.2% and 2.9%, respectively.²⁴ The likely explanation is that other coinherited modifiers (eg, additional risks conferring variant mutations) exist in a pedigree or that select members of some families share extremely high levels of sun exposure histories.

CDKN2A mutation penetrance (or the likelihood of developing melanoma over time) also varies by geography. The estimated penetrance rates are 30%

to 91%, 50% to 76%, and 13% to 58% among patients 50 to 80 years of age in Australia, the United States, and Europe, respectively. These broad risk differences could also be attributed to different sun exposure patterns and the presence of other genetic risk factors in the families.^{25,26} For instance, coinheritance of melanocortin 1 receptor (MC1R) variants and specific interleukin-9 and glutathione S-transferase theta 1 variants have been described as risk modifiers for *CDKN2A* mutation penetrance.^{9,27,28} In a population-based study, Begg et al²⁹ found that the estimated risks of CMM among *CDKN2A* mutation carriers were 14%, 24%, and 28% by 50, 70, and 80 years of age, respectively; the lower risk estimates may reflect the lack of other melanoma risk variants in these sporadic cases.

Various studies have also shown a much lower median age of onset of CMM in patients from germline *CDKN2A* mutation families (33-45 years of age) compared to patients without a *CDKN2A* mutation (53-61 years of age); this trend remains largely consistent regardless of geographic region.^{3,30,31} There are reports of *CDKN2A* kindreds where CMM

has occurred in the early teens and twenties.²⁰ As would be expected, the increased risk of CMM in these patients does not diminish with their first diagnosis because they also have a much higher 5-year cumulative incidence of a second melanoma compared to mutation-negative controls (23.4% and 2.3%, respectively).³²

Germline *CDK4* mutations have also been described in patients with FAMMM syndrome, albeit rarely.³³⁻³⁵ As alluded to above, *CDK4*, which is the target for p16 inhibition, plays an important role in normal cell cycle progression (Fig 2). The oncogenic *CDK4* mutations described in affected families translates into a substitution of arginine-24, which disrupts p16 binding.³⁵ Puntervoll et al³⁶ have reported an increased CMM risk in 17 families from 8 different countries that harbor *CDK4* mutations. Of 103 patients with 1 CMM, 41.7% developed a second primary CMM and 21.1% developed CMM before 30 years of age (median, 39 years of age). In addition, 70% to 75% of patients had multiple atypical nevi, which was considered to be a modifier for CMM risk given that these patients developed CMMs at a younger age.³⁶ This study investigated the clinical phenotype of these *CDK4*-mutant melanoma families and determined that it is indistinguishable from the more well characterized *CDKN2A*-mutant melanoma phenotype (ie, a high burden of atypical nevi, early age of disease onset, and a predilection for multiple primary melanoma).³⁶ Because p16 directly interacts with *CDK4*, it is not surprising that the 2 phenotypes overlap significantly; in essence, the same biochemical event (increased RB1 phosphorylation) occurs with either mutation (Fig 2).

MELANOMA ASTROCYTOMA SYNDROME (OMIM 155755)

Melanoma astrocytoma syndrome (MAS) is a variant of FAMMM that may be more linked to the loss of p14^{ARF} function.³⁷ Larger scale chromosome 9p21 alterations (including deletions involving the *CDKN2A/CDKN2B/CDKN2BAS* gene cluster up to the *MLT3* gene) have been described in some isolated cases.³⁸⁻⁴¹ Kaufman et al⁴² described this syndrome in 1993 when they reported concurrent CMMs and multiple types of nervous system tumors (NSTs) in 8 members of a family over 3 generations. Later, Azizi et al⁴³ reported that 17 individuals with CMM, among 15 families, had ≥1 additional relatives with tumors of the nervous system. Conflicting data exist on this rare syndrome. Patients are generally young (<30 years of age) and can develop CMM either before or after NSTs.^{38-40,44} A positive association between radiotherapy for the NSTs and

the incidence of CMM in these patients has been proposed but remains unsubstantiated.⁴¹

MANAGEMENT OF PATIENTS WITH FAMILIAL ATYPICAL MULTIPLE MOLE MELANOMA SYNDROME, INCLUDING *CDKN2A* CARRIERS

Key points

- Patients with FAMMM syndrome should undergo total body skin examination and dermoscopic examination of clinically atypical nevi with possible total body photography every 3 to 6 months
- Children from families with FAMMM may begin screening in late adolescence
- Because of the reported association between *CDKN2A* mutations and internal organ malignancies (specifically pancreatic cancer), all patients suspected to harbor the mutation should be referred to a specialist for appropriate screening

The significant risk of melanoma inherent to FAMMM syndrome means that these patients need heightened dermatologic surveillance. Some general management considerations for patients with hereditary syndromes are presented in Table III. Given the rarity of melanoma syndromes, most data regarding follow-up recommendations are based on small studies or expert opinion. Given the plethora of clinically atypical moles, dermoscopy is an important tool in approaching patients with FAMMM. It is also prudent for children from families with FAMMM syndrome to undergo routine skin examinations beginning in late adolescence (level of evidence, IV). This recommendation is supported by observational studies showing that patients with FAMMM tend to develop melanomas at much younger ages. Surveillance of patients with FAMMM should entail an extensive baseline total body skin examination (TBSE), including the scalp, oral mucosa, genital area, and nails. Most authors suggest that screening performed at 6-month intervals is adequate,^{10,20,45,46} although formal prospective trials of outcome do not exist (level of evidence, IV). Haenssle et al⁴⁷ have reported that patients with FAMMM may develop up to 1 new melanoma for every 3 years of follow-up and suggest that 3-month interval examinations may be more appropriate. There are no current data supporting the idea that 3-month interval examinations are superior to 6-month interval examinations regarding patient outcomes (level of evidence, IV). Nevi should be checked for any changes in morphology (eg, color or symmetry) and size. Because these patients may

Table III. Recommendations for patients with suspected hereditary melanoma^{3,70,71}

Obtain a thorough medical history from the patient, including:

 Sun exposure patterns

 Personal history of MM or other type of skin cancer (age at diagnosis should be noted)

 History of internal organ malignancies

 Age at diagnosis should be noted

 Should be updated annually

 Special interest: pancreatic, renal, breast, or other rare types of cancer

 Family medical history should include:

 Relatives with multiple and/or atypical nevi

 Sun exposure patterns

 Fitzpatrick skin type/clinical phenotype (eg, red hair, etc)

 Family history of MM (first- and second-degree relatives)

 No. of primary MMs and age at diagnosis should be noted

 Family history of internal organ malignancies (3-generation pedigree)

 Age at diagnosis should be noted

 Should be updated annually

 Special interest: pancreatic, ocular melanoma, mesothelioma, renal, breast, or other rare types of cancer

In cases of positive personal or family history of MM or other cancer, relevant medical information should be obtained (eg, histology reports, medical reports, etc)

Physical examination

 Fitzpatrick skin type/clinical phenotype (ie, red hair, etc)

 No. of banal and atypical nevi (<50 or >50)

 Signs of solar elastosis (eg, lentigines, actinic keratoses, etc.)

 Presence of multiple "Spitzoid" nevi or lesions resembling dermal nevi

 Special attention should be given to examining for atypical features in clinical appearance (eg, the presence of trichilemmomas, various types of minor malformations, etc)

 Dermoscopy should be applied to all nevi

Clinical recommendations

In general, patients and families should be educated in the importance of skin cancer prevention measures (eg, sunscreen, sun avoidance, abstaining from tanning beds, etc)

If patient exhibits multiple banal nevi and has negative personal or family history for MM and/or other cancers:

 Dermoscopic examination should be repeated at least annually

 Total body photography can be considered

If patient exhibits multiple and/or atypical nevi or has positive personal or family history for MM and/or other cancers or if patient exhibits lesions resembling MBAITs:

 Dermoscopic examination should be repeated every 3 to 6 months depending on the clinical phenotype

 Total body photography can be considered at 6-month intervals

Recommend dermatologic evaluation all first- and second-degree relatives

If suspicious lesions present (dysplastic nevi or MBAITs), selection and removal should be made for histopathologic examination

If rapidly changing nevi or new lesions appear, surgical removal and histopathologic examination should be recommended to all patients

If melanoma cancer syndrome suspected, patient should be referred for genetic counseling and possible work-up of internal malignancies

MBAIT, Melanocytic BAP1-mutated atypical intradermal tumor; MM, malignant melanoma.

have many atypical nevi, lesions that stand out, exhibiting the so called "ugly duckling sign," may warrant special attention. Beyond a thorough TBSE, the use of more advanced techniques, such as total body photography (TBP) and sequential digital dermoscopy imaging (SDDI) for patients at extreme risk for melanoma has also been suggested⁴⁸—although the adoption of these procedures may be limited by practice logistics. Moloney et al⁴⁹

reported that in 311 high-risk patients evaluated at 6-month intervals, 38% of postbaseline melanomas were detected using TBP and 39% with SDDI. Importantly, these tools allowed for earlier detection and treatment, both of which are known to impact melanoma outcome.⁴⁹ In the study by Moloney et al,⁴⁹ most of the excised melanomas were categorized as *in situ* tumors, and the ratio of benign to malignant excised lesions was reported to be

1.6:1. In addition, Rademaker and Oakley⁵⁰ have reported that the melanomas diagnosed in patients after TBP and SDDI examination were thinner compared to those diagnosed with clinical inspection (69% with a Breslow thickness <0.75 mm compared to 52%; $P = .0216$). Previous studies have also advocated the benefit of TBP in earlier diagnosis of melanoma.^{51,52} An interesting point, though, is that these studies do not report patient outcomes, and their impact on patient survival is therefore unknown. In addition, the recommendations supported by those studies depend on the notion that earlier recognition of melanomas may lead to overall better patient outcome. A small number of studies have reported evidence to support this.⁵³ However, the exact frequency of follow up (eg, at 3-month, 6-month, or 1-year intervals) is not clear. When planning follow-up visits for high risk patients, 2 factors must be weighed: (1) the psychological burden of having to be examined at specific intervals and (2) the cost effectiveness of this process. Risser et al⁵⁴ reported that the number of biopsy specimens obtained from patients undergoing TBP and clinical inspection was the same. Therefore, the cost effectiveness of TBP use is questionable.⁵⁴ It must be mentioned, however, that patients selected for TBP belong to high-risk groups. In addition, the decision to obtain a biopsy specimen of a suspicious lesion after TBSE, is primarily related to nevus morphology at the time of examination, while TBP relates to morphologic changes over time (ie, morphology changing from a previous examination).⁵⁵ Therefore, in theory, melanomas could be diagnosed earlier if TBP were used. In a recent study by Watts et al,⁵⁶ a cost analysis of the surveillance of high-risk melanoma patients was performed. Watts et al⁵⁶ reached the conclusion that although these patients are indeed more costly with regard to follow-up, it is overall cheaper to screen than having to later treat a stage IV melanoma. It is important, however, to find an ideal position where cost and patient benefit are perfectly balanced.⁵⁶ Patients must be encouraged and taught to perform self-examinations at regular intervals either alone or with the assistance of a spouse or relative. Routine sun protective behaviors must be reinforced at every visit. Screening of all family members of FAMMM kindreds should be encouraged. Preemptive removal of observable stable or benign-appearing nevi is not recommended because the practice has not been shown to reduce melanoma risk meaningfully and is associated with increased morbidity and costs (level of evidence, IV). Isolated lesions that are visually

inaccessible to the patient, such as those on the mid-lower back or scalp, may be removed prophylactically.

The association between PC and FAMMM syndrome is well documented, with an estimated risk 13 to 22 times higher than that of the average population; this risk increases to 38-fold in *CDKN2A*-mutant FAMMM patients.^{20,57,58} PC seems to be the second most commonly observed malignancy in patients with FAMMM who harbor a *CDKN2A* mutation.^{3,59} In a study by Goldstein et al,³ PC was observed in 28% of *CDKN2A*-mutant families compared to only 6% of *CDKN2A*-wild type families. Conversely, 74% of families with PC harbored a *CDKN2A* mutation compared to 33% of “melanoma only” families.³ Another study estimated that 17% of *CDKN2A*-mutant patients would develop PC by 75 years of age.⁶⁰ In general, the mean age of onset for PC ranges from 65 to 71 years of age.^{20,45,61} It is unclear whether the age of onset for PC is lower for patients with FAMMM compared to sporadic cases. Various studies on this topic have reported mixed data, with only 1 study by James et al⁶² showing a statistically significant difference in age of PC diagnosis between the 2 groups. Of note, smoking was a strong confounding factor in this study.^{61,62} Evidence regarding the association of FAMMM and other cancers is more equivocal. Associations with digestive tract, breast, and respiratory tract cancer, among others, have been described; however, *CDKN2A* mutation status does not seem to influence the age of onset in these cancers.^{20,59,60,63}

The role of genetic testing for hereditary melanoma has been somewhat controversial because dermatologic management of individuals with familial melanoma (ie, surveillance and sun protection education) rarely requires knowledge of the patient’s *CDKN2A* status. However, as alluded to above, the melanoma phenotype may be a window to a latent PC risk. Therefore, a basic understanding of genetic risk assessment and counseling is worthwhile, but referral to a genetic counselor for more formal evaluation is preferred, given the time constraints of a busy dermatologic practice. The following are just a sampling of some fundamental discussion points (also outlined in Fig 3).

Does my patient have hereditary melanoma? The individual seeking counseling is known as the proband. Currently, there are no firm criteria that would allow easy diagnosis of a proband with hereditary melanoma. Some have adopted the rule of 3s⁶⁴—ie, 1 individual with invasive CMM along with 2 additional members with either CMM or PC on 1

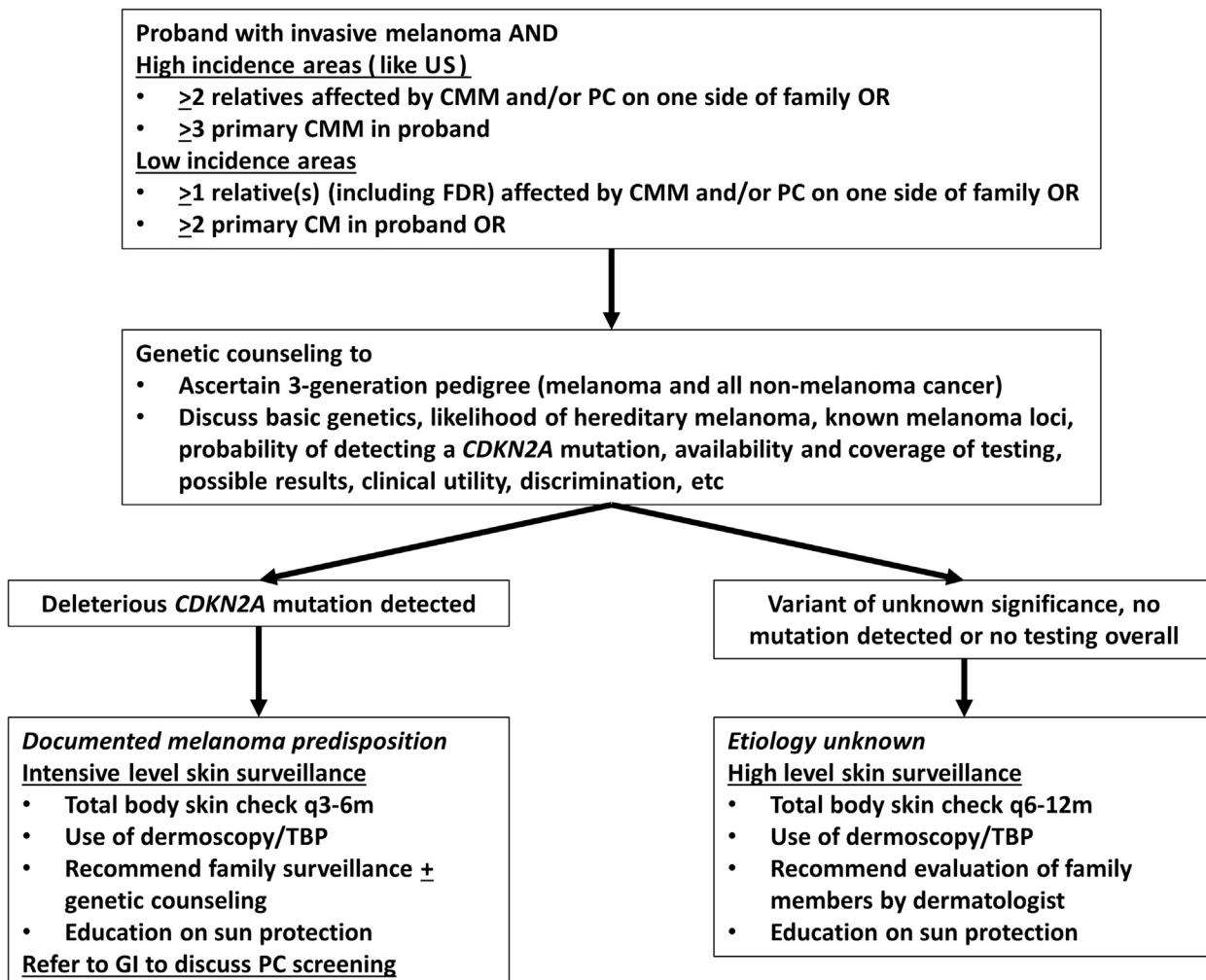


Fig 3. Genetic counseling algorithm for patients with familial atypical multiple mole melanoma (FAMMM). Patients with a personal history of melanoma may be considered for genetic counseling if certain criteria from high and low incidence areas are met. The United States and Australia are high incidence areas; England and Greece are low incidence areas. A genetic counselor would ascertain a 3-generation pedigree and discuss the likelihood of hereditary melanoma, the molecular genetics related to familial melanoma risk, testing options, costs, risks of discrimination, and possible test results. If the patient undergoes *CDKN2A* testing and a deleterious mutation is detected, intensive skin surveillance is recommended, along with a referral to a gastrointestinal specialist for discussion of pancreatic cancer screening. If testing is not pursued or if a normal or variant of unknown significance result is returned, the etiology of the familial pattern remains unknown. Given the family history, the patient is considered high risk and should undergo high level skin surveillance. *CMM*, Cutaneous malignant melanoma; *FDR*, first degree relative; *PC*, pancreatic cancer; *TBP*, total body photography.

side of the family or 1 individual with 3 primary CMMs. One caveat is that severely photodamaged patients may develop 3 melanomas, especially later in life as sun damage accumulates. One perhaps slightly more stringent practical criterion would be a 3 by 40 modification—that is, individuals with 3 CMMs diagnosed before 40 years of age may be more likely to be under genetic influences.

The benefit of formal genetic counseling is the analysis of an in-depth ≥ 3 -generation pedigree. Although dermatologic charts may document a family history of melanoma, other critical information may not be ascertained. For instance, 3 melanoma cases in a small pedigree is different than 3 melanoma cases in a large extensive pedigree. The age of onset, current age, and other concurrent nonmelanoma

cancers all contribute to the final interpretation of hereditary melanoma or mixed cancer syndrome (MCS). The presence of PC in a kindred is also important in assessing genetic risk. Formal training is typically required for accurate pedigree acquisition, and a full family history is essential for accurate risk assessment.

What are the possible genes to be tested? To understand genetic testing, fundamental principles of genetics must first be reviewed. Hereditary melanoma, like nearly all cancer syndromes—with the exception of xeroderma pigmentosum—is autosomal dominant.¹⁹ Therefore, there is a 50% chance of sharing a mutation among first-degree relatives. The major locus to be considered in a patient with FAMMM syndrome is *CDKN2A*, although a small percentage (<1%) of patients with FAMMM harbor *CDK4* mutations. In addition, there are likely many other unknown predisposing loci. Therefore, the first important message is that *CDKN2A* will be normal in a majority of individuals suspected of having FAMMM, especially in areas of high melanoma incidence, such as the United States. This is because there are environmental factors and other genetic factors (whether they be dominant genes or polygenic factors) that have not been discovered.

Who is likely to be a carrier? Phenotypically, the presence of multiple atypical nevi is not enough for the diagnosis of FAMMM, although it has been published that their presence in family members correlates with a 3-fold higher likelihood of carrying a genetic mutation.³³ It is important to note, however, that the presence of atypical nevi is not a carrier signature, because noncarriers, even in *CDKN2A*-mutated families, can have multiple atypical moles. Therefore, there is a complex relationship between melanomas and atypical, or dysplastic, nevi. Two statistical models have been developed in order to assist in identifying *CDKN2A* mutation-bearing individuals or families. MELPREDICT is based on logistic regression, while MelaPRO (which can be obtained as part of CancerGene [<https://www4.utsouthwestern.edu/breasthealth/cagene/>]) incorporates 3 different penetrance models (ie, the Bayes–Mendel algorithm).^{31,32} These models provide a probability of mutation carriage for any given proband (MELPREDICT) or family member (MelaPRO) based on the family cancer pattern. Cancer risk counselors usually have access to MelaPRO as other similar algorithms, such as BRCAPRO for determining BRCA1/2 carrier risk, have been part of the counseling practice.

What are the possible results? The identification of a deleterious *CDKN2A* mutation (a “positive

result”) establishes a disease-causing mutation in the kindred. First-degree relatives (ie, parents, siblings, and children) will have a 50% chance of harboring the same mutation and risk. Penetrance is never 100%, and therefore there will be carriers in the family who may not develop melanoma although the risk will be substantially higher than population rates. If unaffected relatives undergo subsequent testing and are found to have a normal *CDKN2A*, their risks may still elevated because of other risk factors, such as an MC1R variant or excessive sun exposure. However, a noncarrier will have a substantially lower risk of malignancy than a carrier—although it may not return to general population risk levels.

In an affected patient with FAMMM who returns a normal *CDKN2A* result (a “negative result”) or a variant of unknown significance, little advice can be offered. The patient may harbor a high-risk mutation in an undiscovered gene, and therefore the risk is incalculable. These patients should continue to undergo the same dermatologic surveillance. For a nonaffected member of a FAMMM kindred, there is no role for genetic testing without concomitant evaluation of at least 1 if not 2 other affected relatives from the same family. In short, the designation of carrier vs. noncarrier can only be made if the familial mutation can be identified.

How can I use the results? *CDKN2A* mutation carriers should be referred to a health care provider familiar with PC screening⁶⁵ (level of evidence, IV) in addition to ongoing intensive dermatologic surveillance at 3- to 6-month intervals with the possible use of TBP. Relatives of *CDKN2A* mutation carriers, regardless of genetic test results, should continue to be under careful dermatologic surveillance and strict sun protection.

No low-cost, criterion standard screening approach exists for PC, although studies in high-risk cohorts have shown that early, preinvasive pancreatic lesions can be detected with screening programs and then treated preemptively.⁶⁶ Although PC screening lies outside the purview of dermatologists, familiarity with the available screening modalities is useful. Currently, these include endoscopic retrograde cholangiopancreatography (ERCP), which is able to detect small tumors but has associated complications because of its invasive nature; computed tomography and magnetic resonance imaging, which are less sensitive but also less invasive; and endoscopic ultrasound (EUS), which is the most sensitive and safe option at this time⁶⁷ (level of evidence, IV). Some authors suggest that screening should start at 50 years of age or 10 years earlier than the PC age of

onset in the family, but no specific consensus exists for a specific protocol in cancer screening of *CDKN2A* mutation carriers.¹³ Patients with FAMMM who forego testing, test negative for *CDKN2A*, or who have a variant of unknown significance should remain under careful dermatologic surveillance, but PC screening is probably not necessary.

How will the patient use the results? Families in general share exposure risks (eg, sunny vacations together), risk-conferring traits (eg, sun-sensitive skin or blue eyes), and disease-causing variants (eg, *CDKN2A* mutation). The lack of a high-risk mutation in *CDKN2A* should not empower patients to abandon sun protective practices. Parents should also recognize that their children will continue to need strict sun protection even in the face of a normal *CDKN2A*. "True negatives," however, would not need to undergo PC screening. There are various psychological benefits from undergoing genetic testing in *CDKN2A* families, including decreased anxiety.⁶⁸

Will my patient experience genetic discrimination? In 2008, the US Government passed the Genetic Information Nondiscrimination Act (GINA; <http://www.ginahelp.org>) which protects all individuals from health and employment discrimination based on genetic information. The GINA went into effect in 2009 and provides comprehensive protection against genetic discrimination for all Americans. Under GINA, it is against the law for most health insurers to use genetic test results or family history information as a preexisting condition. In addition, under the GINA law, most health insurers cannot use genetic information to make decisions regarding eligibility, premiums, underwriting, or coverage. It is also against the law for employers with ≥ 15 employees to use genetic information in hiring, firing, promotion, or other employment decisions. GINA does not protect against discrimination from life insurance, disability insurance, or long-term care insurance companies. GINA's protections do not apply to the US military or employees of the federal government who get care through the Federal Employees Health Benefits Plans; however, these groups have their own policies in place that may protect their members from insurance discrimination. For more information about the protections offered by GINA, visit www.ginahelp.org.

In conclusion, malignant melanoma pathogenesis is multifactorial and complicated. However, hereditary cancer syndromes, such as FAMMM, provide excellent genetic models for studies that may increase early detection rates and improve existing prevention and management protocols. Patients with a high nevus count and multiple

atypical nevi should always be asked about personal or family history of melanoma or other internal organ cancer. Considering that $\leq 10\%$ of melanomas may be familial, increased physician awareness can lead to faster diagnosis of melanomas and, through patient education, to improved preventive behaviors.

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Hereditary melanoma: Update on syndromes and management

Emerging melanoma cancer complexes and genetic counseling

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Learning objectives

After completing this learning activity, participants should be able to describe algorithms used to assess patients with possible melanoma tumor syndromes (MTS), explain the genetic basis of MTS predisposition, in light of novel susceptibility genes identified recently in genomic studies; discuss the role of genetic testing and genetic counseling in patients with MTS; and determine when it is appropriate to refer patients with MTS.

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Recent advances in cancer genomics have enabled the discovery of many cancer-predisposing genes that are being used to classify new familial melanoma/cancer syndromes. In addition to *CDKN2A* and *CDK4*, germline variants in *TERT*, *MITF*, and *BAP1* have been added to the list of genes harboring melanoma-predisposing mutations. These newer entities may have escaped earlier description in part because of more advanced technologies now being used and in part because of their mixed cancer phenotype as opposed to a melanoma-focused syndrome. Dermatologists should be aware of (and be able to recognize) the clinical signs in high-risk patients in different contexts. Personal and family histories of cancer should always be sought in patients with multiple nevi or a positive history for melanoma, and should be updated annually. Various features that are unique to specific disorders, such as the appearance of melanocytic *BAP1*-mutated atypical intradermal tumors in cases of *BAP1* melanoma syndrome, should also be recognized early. These patients should be offered regular screenings with the use of dermoscopy and total body photography, as needed. More importantly, referral to other specialists may be needed if a risk for internal malignancy is suspected. It is important to have in mind that these patients tend to develop multiple melanomas, along with various internal organ malignancies, often at younger ages; a multidisciplinary approach to their cancer screening and treatment is ideal. (J Am Acad Dermatol 2016;74:411-20.)

Key words: *BAP1*; familial melanoma syndrome; melanoma genetics; *MITF*; mixed cancer syndromes; *PTEN*; *TERT*.

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GENERAL CONSIDERATIONS FOR EMERGING MELANOMA CANCER COMPLEXES

Key point

- A number of melanoma susceptibility genes have been discovered in recent years, including mutations in BAP1, MITF, shelterin complex, and PTEN

During the last few years, sequencing efforts in the field of melanoma research have led to a number of scientific breakthroughs, including the elucidation of unknown molecular pathways and the discovery of new susceptibility genes. These discoveries hold great value because they may assist in the identification of possible molecular therapeutic targets or could serve as biomarkers for melanoma development and progression. Although the identification of new susceptibility genes may shed a light on the complexity of the genetic landscape of melanoma, how these genes influence patient phenotypes has not been determined. Overall, it is estimated that about 10% of melanoma patients present with a positive family history for melanoma.¹ However, true hereditary melanoma syndromes are much rarer. Patients often present with early onset melanomas, multiple primary melanomas, and a family history that features multiple cases of melanoma in several generations on one side of the family.² In addition, a number of those patients (and their families) may present with other internal organ malignancies. These patients fall under the category of “mixed cancer syndrome” patients, where melanoma may appear in the context of a more general predisposition for malignancy. Familial atypical multiple mole melanoma syndrome is one of the most comprehensively described melanoma tumor syndromes. However, in recent years, mutations in BRCA1-associated protein 1 (BAP1), shelterin complex, microphthalmia-associated transcription factor (MITF), and phosphatase and tensin homolog (PTEN) have also been associated with melanoma and internal organ cancers. Part II of this continuing medical education article summarizes the current knowledge of these emerging cancer complexes, their pathogenetic mechanisms, and the known data regarding patient phenotypes. We also provide information regarding the management of these patients.

BAP1 TUMOR SYNDROME

Key points

- BAP1 tumor syndrome is associated with the appearance of cutaneous melanoma, uveal melanoma, and various internal malignancies

- Up to 67% of patients with BAP1 cancer complex present with multiple melanocytic BAP1-mutated atypical intradermal tumors
- Patients presenting with metastatic uveal melanomas or concurrent uveal and cutaneous melanomas have a higher possibility of exhibiting BAP1 mutations compared to other patients with melanoma

Somatic mutations of *BAP1* were first described in 26 of 31 aggressive (class 2) cases of uveal melanoma (UM).^{3,4} Subsequently, germline *BAP1* mutations were also reported in multicancer families. Cutaneous/ocular melanomas, melanocytic proliferations, and other internal neoplasms are a part of the BAP1 cancer complex, and the term COMMON syndrome has therefore been proposed.⁵ This cancer complex is phenotypically characterized by the appearance of clinically benign but histologically aggressive melanocytic skin tumors (Fig 1, A and B) at a young age, along with a high incidence of mesothelioma, UM, cutaneous melanoma, and possibly other cancers at older ages. Although a single germline *BAP1* mutation was reported in the original paper by Harbour et al,⁴ the association of germline *BAP1* mutations with a multitude of cancers was independently described in families with UM and mesothelioma⁶ and in kindreds with both UM and cutaneous melanoma.⁷

Aspects of the pathogenesis of BAP1 tumor syndrome

BAP1 is located on chromosome 3 (3p21.3), and it encodes the 90-kDa BAP1 protein (Fig 2, A). Enzymatically, BAP1 has an ubiquitin carboxy-terminal hydrolase domain, suggesting that it serves as an intracellular deubiquitinase.⁸ Ubiquitin groups are small peptides used to posttranslationally modify proteins in order to target them for degradation by proteasomes or to regulate its function. BAP1 has roles in many important cellular processes, including cell division, gene expression, signal transduction, protein trafficking, dsDNA repair, and DNA repair regulation, among others.^{8,9} The pathogenetic mechanisms through which *BAP1* mutations (ie, rearrangements, homozygous deletions, and missense mutations) directly or indirectly promote melanomagenesis have not been fully elucidated. Some authors have suggested that patients with the mutation may exhibit altered patterns of gene expression through histone 2A modification¹⁰ or impaired DNA damage repair in response to ultraviolet light (UV)-induced damage.⁸ However, the role of UV radiation in the appearance of UM is debatable.¹¹ BAP1 is also a UV-inducible substrate of



Fig 1. The BAP1 tumor syndrome phenotype. **A**, Patient with germline BAP1 mutation. Clinically atypical moles may or may not be present. **B**, Typical melanocytic BAP1-mutated atypical intradermal tumors (MBAITs). These lesions are usually round, dome-shaped, and orange to red in color. **C**, Pedigree of a BAP1 kindred. Proband (arrow) had multiple MBAITs along with early onset cutaneous melanoma (MEL), squamous cell carcinoma, and basal cell carcinoma. Her brother had early onset kidney cancer (KID) and cutaneous melanoma along with many MBAITs. Her sister has had multiple MBAITs and cutaneous melanoma; her father had lung cancer (LUNG CA) and ocular melanoma (OC MEL). Carriers are indicated by (m). This family was studied by Njauw et al.⁵ **D**, Patients with the BAP1 tumor syndrome are at risk for cutaneous melanoma, MBAITs, ocular melanoma, mesothelioma, and possibly other lung cancers and renal cell cancer.

the ataxia telangiectasia mutated (ATM) and ataxia telangiectasia and Rad3-related (ATR) kinases. These 2 kinases inhibit cell cycle progression after UV damage in order to allow for either DNA repair or the induction of apoptosis.¹² Interestingly, a recent study by Kumar et al³ showed that BAP1 may have a tumor maintenance role in sporadic cutaneous malignant melanoma (CMM).¹³ More studies are needed to fully understand the precise carcinogenic mechanisms of *BAP1* mutations.

Phenotype of patients with BAP1 tumor syndrome

Patients with BAP1 tumor syndrome develop multiple, distinct, melanocytic lesions. These lesions have been described as skin-colored to reddish-brown, dome-shaped to pedunculated, well circumscribed papules that appear progressively after the first decades of life (Fig 1, B).⁹ They range from 2 to 10 mm in diameter and may number from 5 to >50.⁷ These skin tumors have been reported to

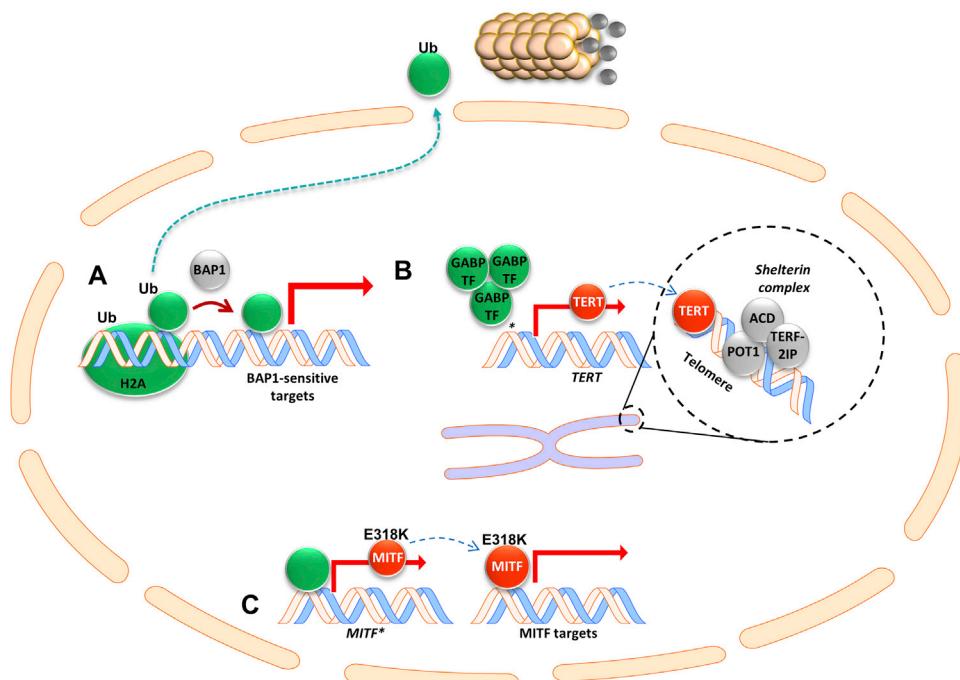


Fig 2. New melanoma predisposition pathways. **A**, In the BAP1 pathway, the deubiquitinase activity of BAP1 removes ubiquitin (Ub) groups from transcriptional regulators and histone 2A (H2A), thereby regulating gene expression. Inactivating mutations in BAP1 leads to the loss of nuclear BAP1 activity. **B**, Both telomerase (TERT) and the shelterin complex maintain normal telomeric structure. Inherited or somatic variants in the TERT promoter region recruits GA-binding protein transcription factor to the TERT promoter, stimulating TERT transcription. Inactivating mutations in other shelterin complex genes (eg, POT1) can be inherited, disrupt normal telomere structure, and predispose individuals to melanoma. **C**, Finally, the E318K mutation in MITF removes a normal sumoylation site in MITF, altering the occupancy and transcription of MITF target genes. Presumably, changes in the expression pattern of MITF target genes, which can regulate the survival and the pigment synthetic genes in melanocytes, increase melanoma risk. GABP TF, GA-binding protein transcription factor; H2A, histone 2A; Ub, ubiquitin group.

resemble dermal nevi clinically and nevoid melanomas⁵ or atypical Spitz tumors (ASTs) histologically. However, Carbone et al⁸ evaluated the histologic and molecular characteristics of these tumors and reported that their morphology was that of a conventional junctional, compound, or dermal nevus composed of small melanocytes that lack BAP1 staining.⁸ In addition, a dermal lesion composed of large epithelioid BAP1-negative (and, occasionally, BRAF-mutated) melanocytes (ie, no mitoses, negative Ki67 immunostaining) have been described adjacent to these lesions, although no Kamino bodies were seen. The authors proposed the term melanocytic BAP1-mutated atypical intradermal tumors (MBAITs) to describe these latter lesions.⁸ These characteristics may be useful in differentiating ASTs from MBAITs, although the line of distinction is often blurred. Wiesner et al,¹⁴ after investigating 32 sporadic ASTs, reported that 9 (28%)

had a loss of BAP1 expression, of which 8 (89%) had concomitant BRAF mutations, and had a very similar histologic picture to that of MBAITs. Some dermatopathologists therefore consider MBAITs a subgroup of ASTs that feature the loss of BAP1.

In a recent study, 66.7% of patients with germline *BAP1* mutations had MBAITs, compared to none of the controls. Also, some of the investigated patients that were positive for MBAITs had already been diagnosed with CMM.¹⁵ Interestingly, these tumors are considered to be slow growing, benign, and to possess low metastatic potential.^{9,15} Unfortunately, no data exist regarding the median age of onset for MBAITs and CMM in this cohort. However, because these lesions can appear early in life, they should be viewed as potential markers of germline *BAP1* mutagenesis. There is insufficient evidence to fully exonerate these lesions as being premalignant.

Table I. Malignancies (aside from melanoma) associated with familial melanoma syndromes or cancer syndromes with higher incidence of melanoma^{3-8,15,19,24,25,35,37,41,42,49-52}

BAP1	PTEN	TERT	MITF	Shelterin complex (ACD and TERF2IP)
Uveal melanoma*	N/A	N/A	N/A	N/A
Basal cell carcinoma	N/A	N/A	N/A	N/A
Breast cancer	Breast cancer*	Breast cancer	Breast cancer	Breast cancer
Ovarian tumors		Ovarian tumors	N/A	Ovarian tumors
N/A	Endometrial cancer*	N/A	N/A	Cervical cancer
Pancreatic cancer	N/A	Pancreatic cancer	Pancreatic cancer	N/A
N/A	N/A	N/A	N/A	N/A
Colon cancers	Colorectal carcinoma*	Colon cancers	N/A	Colon cancers
Mesothelioma, lung cancer*	N/A	Lung cancer	N/A	Lung cancer
N/A	N/A	Acute myeloid leukemia, chronic lymphocytic leukemia, and myelodysplastic syndrome	N/A	Leukemia
N/A	N/A	N/A	Lymphoma	B-cell lymphoma
Meningioma, paraganglioma, and neuroendocrine carcinoma	N/A	Central nervous system tumors	N/A	Meningioma and brain tumors
Renal cell carcinoma*	Renal cell carcinoma	Renal cell carcinoma	Renal cell carcinoma*	Renal cell carcinoma
N/A	N/A	Urinary bladder carcinoma	N/A	Urinary bladder carcinoma
N/A	N/A	Prostate cancer	N/A	Prostate cancer
N/A	N/A	Testicular cancer	N/A	N/A
Hepatic cholangiocarcinoma	N/A	N/A	N/A	N/A
N/A	N/A	N/A	N/A	Uterine tumors
N/A	N/A	N/A	N/A	Ovarian tumors
N/A	N/A	N/A	N/A	Cancer of the esophagus
N/A	Thyroid gland carcinomas (follicular and papillary types)*	N/A	N/A	N/A

ACD, Adrenocortical dysplasia; BAP1, BRCA1-associated protein 1; MITF, microphthalmia-associated transcription factor; N/A, not available; PTEN, phosphatase and tensin homolog; TERT, protein component of telomerase.

*Characteristic tumors.

Melanomas in BAP1 tumor syndrome and patient management

BAP1 tumor syndrome has been clearly associated with a higher incidence of CMM and UM. Njauw et al⁵ have shown that *BAP1* mutations are more frequent among metastatic UM cases compared to nonmetastatic UM controls (8% vs 0%; $P = .059$), which has subsequently been confirmed in a separate cohort of 507 patients with UM.¹⁶ In addition, *BAP1* mutations were more common in families with both CMM and UM compared to those with only CMM (29% vs 0.52%; $P = .003$).⁵ Gupta et al¹⁶ have recently reported that patients with UM who are

positive for germline *BAP1* mutations developed larger tumors (mean diameter, 15.9 vs 12.3 mm), had higher rates of ciliary body involvement (75.0% vs 21.6%), had a higher metastatic potential (71.4% vs 18.0%), and had an increased frequency of family cancer history (especially for CM and UM) compared to controls. Carbone et al¹⁵ have also reported that 17.7% and 12.9% of the *BAP1*-mutant patients in their study developed CMM and UM, respectively, compared to none of the controls. Beyond these select studies, many more have demonstrated an association between CMM and *BAP1* mutations.^{7,17-20} Given the aggressive histologic

Table II. Summary of known data on the phenotypic appearance of patients with possible melanoma tumor syndromes^{5,7,15,30,33,38-40,45,47,48}

Characteristics	BAP1	TERT	POT1	PTEN (Cowden syndrome)	MITF
Incidence	Unknown	Unknown	Unknown	1:200,000	Unknown
Phenotype	Multiple MBAITs (appear during first decades of life)	Multiple atypical nevi (possible)	Not clearly defined (mutation is rare)	Trichilemmomas, papillomatous papules, mucosal lesions (papules), and palmoplantar keratosis	Fair skin type (debated); multiple atypical nevi
Characteristics of melanoma	Melanoma: clinical appearance remains undefined; uveal melanoma: aggressive course with high metastatic potential	Nodular or superficial spreading types	Clinical appearance remains undefined	Clinical appearance remains undefined	Amelanotic melanoma may be more common in this population
Age of onset	Current data do not indicate earlier age of onset	Age of onset is not described	Early age of onset	Age of onset is not described	Early age of onset
Multiple primary melanomas	Yes	Yes	Yes	Unknown	Yes

BAP1, BRCA1-associated protein 1; MBAIT, melanocytic BAP1-mutated atypical intradermal tumor; MITF, microphthalmia-associated transcription factor; POT1, protection of telomere 1; PTEN, phosphatase and tensin homolog; TERT, protein component of telomerase.

appearance of MBAITs, some of these CMMs could have been misdiagnosed MBAITs. More studies are needed to understand the clinical features and course of BAP1-associated CMMs.

Given the rarity of BAP1 tumor syndrome, there are no codified recommendations for the management of patients with *BAP1* mutations. It is extremely important for known *BAP1* mutation carriers to be closely monitored with at least biannual skin examinations accompanied by removal of all changing lesions^{9,15} (level of evidence, IV). MBAITs can appear completely banal (Fig 1, B), but should be completely excised given the frequently atypical histology. If a patient presents with multiple MBAITs, lesions that show atypia or morphologic changes over time should be excised (level of evidence, IV). Moreover, an annual ophthalmologic screening starting from early adulthood would be appropriate (level of evidence, IV).

BAP1 tumor syndrome and other cancers

An example of a *BAP1* mutation-positive family pedigree is shown in Fig 1, C. *BAP1* mutations have also been associated with a number of other types of malignancy (Table I). Overall, Carbone et al¹⁵ have reported that 63.5% of patients with *BAP1* mutations (compared to 9.1% of controls) developed at ≥ 1 cancer (odds ratio, 17.39 [95% confidence interval {CI}, 6.07-49.83]). As with other cancer syndromes, these patients are also at risk for developing

malignancies at a younger age. No specific screening protocols for internal malignancies have been currently established for individuals who carry a germline *BAP1* variant.

TELOMERES AND MELANOMA RISK

Key points

- The shelterin complex and telomerase protect telomeres from gradual erosion, a process that leads to cell senescence
- Mutations in TERT, the protein component of telomerase, and in various components of the shelterin complex have been associated with a higher incidence of melanoma and other internal malignancies
- The association of these mutations with inherited melanoma syndromes remains to be elucidated

Telomeres are DNA protein structures comprised of tandem repeats of the 6-nucleotide unit sequence TTGGG that extend for thousands of bases at chromosome ends. As DNA replication mechanisms are unable to fully copy end DNA, a progressive shortening of telomeres is observed with subsequent cycles, which eventually leads to cell senescence. However, various mechanisms exist in order to counter this gradual telomere erosion.²¹ The shelterin complex physically protects telomeres and also regulates the function of *TERT*. The shelterin complex contains 6 proteins: telomere repeat factor

1 (TRF1), TRF2, and TPP1, which can specifically recognize and bind to double-stranded TTAGGG repeats; protection of telomere 1 (POT1), which binds to the single-stranded telomeric overhang; and TRF1- and TRF2-interacting nuclear protein 2 (TIN2) and repressor/activator protein 1 (RAP1; Fig 2).²² POT1 mutations lead to insufficient capping of telomeres by shelterin. In addition, overexpression of POT1 leads to inhibition of telomerase function. Interestingly, POT1 and TPP1 may have the ability to serve as enhancers of telomerase processivity.²³

TERT, a reverse transcriptase, and TERC, an RNA fragment that acts as a template for telomere addition, are the main components of telomerase, a large multisubunit ribonucleic protein (Fig 2, B). Telomerase protects telomeres by elongating them via a strict cell cycle-regulated process. In addition, telomerase can preferentially elongate the shortest telomeres, which leads to only a subset of telomeres being elongated in any given cell cycle. Telomerase levels and the balance between its components play an important role in appropriate telomere length maintenance.²⁴

Mutations in the promoter region of *TERT* have been described both at the germline level and at the somatic level in sporadic cases of melanoma.^{25,26} These mutations have been found in the promoter region of the *TERT* isoform that encodes a catalytic reverse transcriptase subunit of telomerase responsible for telomere length maintenance (Fig 2, B). Indeed, an association between longer telomere length and CMM risk has been shown;²⁷ telomerase overexpression may be responsible for the cellular immortality associated with cancer.^{25,26} Horn et al²⁵ have described *TERT* mutations in a kindred with 14 CMM patients, yet they also described somatic mutations of *TERT*, which bore a clear UV signature, in sporadic CMMs.²⁵ A paucity of data exists on the phenotypes of patients carrying *TERT* mutations, although the coexistence of numerous nevi has been reported.²⁵ Several studies have identified UV signature mutations at various positions in the *TERT* promoter.^{25,26} These alterations may increase the transcription of *TERT* by creating novel Ets transcription factor binding sites. The GA-binding protein (GABP) transcription factor, an Ets family member, has now been shown to be recruited to the sites of *TERT* promoter mutations.²⁸ As reported in a recent study, melanomas with *TERT* promoter variants were more likely to be nodular and superficial spreading in subtype and had increased thickness, ulceration, high mitotic rate, and frequent BRAF^{V600E} mutations.²⁹ It is uncertain whether these characteristics also apply to familial cases, but they do imply a more

aggressive course for these CMMs.²⁹ In a recent study by Gibbs et al,³⁰ a significant association between multiple primary melanomas and mutations in *TERT* has been demonstrated (*TERT/CLPTM1L* rs401681; $P = .004$). Aside from CMM, a number of other malignancies have been attributed to *TERT* mutations (Table I). Interestingly, similar mutations were seen in 16% of various established cancer cell lines, suggesting that this might be a common activating mutation in multiple cancer types.²⁶ In addition, Vinagre et al³¹ observed recurrent *TERT* promoter somatic mutations in 43% of central nervous system cancers, 59% of bladder cancers, and 10% of thyroid (follicular cell-derived) cancers in a total of 741 tumors screened.³¹

Other studies have also connected the *TERT* locus or telomere biology with melanoma risk.³² Nan et al³³ researched the role of 39 single-nucleotide polymorphisms (SNPs) associated with telomere length in 218 patients with CMM and found a positive association with telomere length and CMM risk. In addition, 2 SNPs in the *TRF2* gene, rs153045 and rs251796, showed significant associations with both total number of moles and the number of raised moles on upper extremities.³³ This finding is consistent with those of previous studies.³⁴ Iles et al³⁵ studied 7 SNPs that were previously associated with telomere length in 11,108 patients with CMM and 13,933 controls from various areas in the world. A strong association between increased telomere score and increased risk of melanoma ($P = 8.92 \times 10^{-9}$) was consistent across geographic regions, and 4 SNPs with a P value $<.05$ were reported (rs10936599 [*TERC*], $P = .0003$; rs2736100 [*TERT*], $P = .02$; rs7675998 [*NAFI*], $P = .03$; and rs9420907 [*OBFC1*], $P = .001$).³⁵ The frequency of these mutations in melanoma kindreds has not yet been investigated.

Beyond telomerase, other components of the telomeric apparatus have also been shown to harbor mutations in melanoma-prone families. POT1 is a critical member of the shelterin complex, which resides at the telomeres and protects the ends of chromosomes. Mutations in *POT1* have been described in a small number of unrelated Italian, French, and US families with melanoma.^{36,37} In addition to *POT1* mutations, other mutations affecting the function of the shelterin complex have also been described. For instance, mutations in the adrenocortical dysplasia (*ACD*) gene have been observed in a small number of melanoma families. This gene not only increases the affinity of POT1 for telomeric single-stranded DNA, but, together with POT1, mediates the interaction between shelterin and *TERT* as well. Other mutations of the shelterin

complex observed in CMM families include mutations in *TERF2IP*. Families harboring such mutations may present with early onset melanomas (appearing in patients as young as 15 years of age) and multiple primary melanomas. Other types of cancer were also noted, including breast, prostate, and lung cancers, among others³⁸ (Table I).

OTHER MELANOMA CANCER SYNDROMES

Key points

- Cowden syndrome belongs to the family of PTEN hamartoma tumor syndromes and is characterized by the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules), and palmoplantar keratosis within the 3 first decades of life
- Newer data suggest that Cowden syndrome patients have a higher risk of presenting with melanoma compared to healthy controls
- Patients that harbor *MITF* mutations may exhibit a high atypical nevus count and have a tendency to develop melanomas at a young age
- Patients with pancreatic or renal cancer who harbor *MITF* mutations have a higher risk of developing CMM

PTEN hamartoma tumor syndrome (PHTS) is a rare condition that encompasses 4 major, clinically distinct entities associated with germline mutations in the tumor suppressor gene *PTEN*. These include Cowden syndrome (CS), Bannayan-Riley-Ruvalcaba syndrome, Proteus syndrome, and Proteus-like syndrome. Phenotypically, all of them are characterized by the formation of multiple hamartomas caused by unregulated cellular proliferation, but only CS seems to be associated with an increased risk for malignancy.^{39,40} CS is rare, with an estimated prevalence of approximately 1 case per 200,000 population.⁴⁰

CS exhibits a distinct phenotype that includes the appearance of trichilemmomas, papillomatous papules, mucosal lesions (papules), and palmoplantar keratosis. These features are pathognomonic, because 99% of the patients develop them before the third decade of life (diagnostic criteria appear in Pilarski et al³⁹ and Hobert and Eng⁴⁰). Although CS has been associated in the past with various types of malignancies, recent data also show an association with melanoma. Tan et al⁴¹ investigated 368 individuals carrying *PTEN* mutations and demonstrated an elevated standardized incidence ratio for CMM of 8.5 (95% CI, 4.1-15.6), with an estimated lifetime risk of 6%. Similarly, Bubien et al⁴² reported

a standardized incidence ratio for melanoma of 28.3 for women (95% CI, 7.6-35.4), and 39.4 for men (95% CI, 10.6-100.9; $P < .001$) in 154 investigated patients. At this point, the exact incidence of melanoma in patients with CS has not been clearly defined. Therefore, an annual dermatologic examination should be considered for all patients with CS (level of evidence, IV). For patients with documented germline *PTEN* mutations, referral to specialized centers for coordinated cancer care (eg, annual thyroid gland ultrasonography, mammography, or endometrial biopsy) is recommended³⁹ (level of evidence, IV). Given the rarity of CS, most recommendations are supported on anecdotal data or small studies.

A single codon 318 Glu-to-Lys (E318K) mutation in *MITF* was recently described and shown to increase CMM risk.⁴³⁻⁴⁵ *MITF* has been shown to act both as a master transcription factor involved in cell cycle regulation and a transcriptional repressor.⁴⁶ The E318K mutation affects *MITF* sumoylation (Fig 2, C), thereby altering the transcriptional properties of *MITF*.⁴³ Recently, Bartolotto et al⁴³ reported that *MITF* (E318K) mutations are associated with a 5-fold increase in the risk for developing CMM, renal cancer, or both. Ghiotto et al⁴⁴ similarly reported that *MITF* (E318K) mutation carriers have a 3-fold increase in CMM risk; the authors also determined that there was a positive association with the development of other types of cancer (Table I). Interestingly, carriers with a personal or family history of pancreatic cancer or renal cancer had a 31- and 8-fold increase in risk, respectively, for developing CMMs.⁴⁴ Yokoyama et al⁴⁵ studied the phenotypic traits of *MITF* (E318K) mutation carriers and reported an association with a higher nevus count, CMM onset before 40 years of age, and nonblue eye color; no association was found with freckling, skin color, or hair color. These findings were corroborated by Sturm et al,⁴⁷ in addition to a reportedly higher incidence of amelanotic melanoma and an association with fair skin. These patients had not only a higher nevus count, but also more nevi >5 mm in diameter compared to controls. The most common location of CMM development was the back, followed by the limbs, which as the authors suggested may indicate a propensity for sites exposed to UV radiation. The predominant dermoscopic pattern for the nevi in *MITF* (E318K) mutation carriers was reticular.⁴⁷ The exact incidence of *MITF* (E318K) mutation is not defined in the overall population. However, this variant has been found to be augmented in cases featuring multiple primary melanomas and in those with a family history of melanoma.⁴⁸ Although most

studies largely corroborate one another, additional studies are needed in order to fully understand the way that these mutations alter the risk for cancer development and the clinical utility of testing for this single variant. A summary of the basic known clinical characteristics for emerging melanoma syndromes can be seen in Table II.

In conclusion, a number of genes associated with melanoma have been described in recent years. However, the pathogenesis of melanoma is complicated and multifactorial, and it is likely that many contributory genes remain to be elucidated. With high throughput next generation sequencing and big data analysis, the science of melanoma syndromes is fluid and changing. Dermatologists therefore need to be constantly aware of new cancer complexes involving CMM in order to provide early diagnosis for cutaneous malignancies and referral to specialized centers for preventive interventions to screen for possible internal malignancies. Recognizing and treating such patients requires a multidisciplinary approach that includes, among others, dermatologists, pathologists, and oncologists. More epidemiologic, clinical, and genetic studies are needed in order to fully understand the way that these syndromes are inherited, the role of environmental factors in gene penetrance, the influence of gene-gene interactions, and the importance of these genes in patient prognosis. In addition, such studies may also assist in identifying new drug targets for the treatment of melanoma.

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Familial skin cancer syndromes

Increased melanoma risk

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Learning objectives

After completing this learning activity, participants should be able to describe the appropriate screening of patients at risk for inherited melanoma risk; list resources for ordering genetic tests for patients who are at increased risk for melanoma; and develop an appropriate management plan for patients with a germline predisposition to melanoma.

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Phenotypic traits, such as red hair and freckling, increase melanoma risk by 2- to 3-fold. In addition, approximately 10% of melanomas are caused by inherited germline mutations that increase melanoma risk from 4- to >1000-fold. This review highlights the key genes responsible for inherited melanoma, with an emphasis on when a patient should undergo genetic testing. Many genetic syndromes associated with increased melanoma risk are also associated with an increased risk of other cancers. Identification of these high-risk patients is essential for preventive behavior reinforcement, genetic counseling, and ensuring other required cancer screenings. (J Am Acad Dermatol 2016;74:423-34.)

Key words: genetics; genetic syndromes; inherited cancer risk; melanoma; oncogenes; skin cancer; tumor suppressor.

INTRODUCTION

Key points

- Hereditary melanomas account for 5% to 12% of all melanoma cases
- Individuals with hereditary melanoma may have an increased risk of internal cancers, such as pancreatic cancer or central nervous system tumors
- Clinical criteria for genetic testing include both individual and family factors

- Individuals with a strong family history of melanoma are still at increased risk of melanoma regardless of whether they are found to carry a known melanoma-associated mutation

Malignant melanoma (MM) represents only 5% of all new skin cancer diagnoses but accounts for the majority of skin cancer deaths.¹ MM incidence is rising worldwide, contributing to a significant

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Abbreviations used:

ACD:	adrenocortical dysplasia homologue
BAP1:	BRCA1-associated protein-1 (ubiquitin carboxy-terminal hydrolase)
CDKN2A:	cyclin-dependent kinase inhibitor 2A
CDK4:	cyclin-dependent kinase 4
LFS:	Li–Fraumeni syndrome
MM:	malignant melanoma
MCR1:	melanocortin 1 receptor
MITF:	microphthalmia-associated transcription factor
POT1:	protection of telomeres 1
PTEN:	phosphatase and tensin homolog
TERT:	telomerase reverse transcriptase
TERF2IP:	telomeric repeat binding factor 2, interacting protein
UV:	ultraviolet
XP:	xeroderma pigmentosum

health care burden.¹ In addition to environmental exposures and phenotypic traits, such as nevus count, red hair, and freckling, heritable genetic risk factors can contribute significantly to MM risk in affected individuals.² An estimated 5% to 12% of all worldwide melanomas are estimated to be caused by inherited, high-penetrance, germline mutations, each with distinct clinical hallmarks (Table I).³

Genetic alterations typically increase cancer risk via 3 major mechanisms: the activation of oncogenes, the loss of tumor suppressor genes, or increased chromosomal instability.⁴ In oncogene activation, a mutation in 1 copy of a gene creates a constitutively active protein, promoting cell proliferation.⁴ Most oncogene-related cancer syndromes are inherited in an autosomal dominant manner or occur sporadically, as is the case with gain of function mutations in the proto-oncogene *RET*, which leads to development of the multiple endocrine neoplasia syndromes.⁵

Tumor suppressor genes encode proteins that function normally to limit cellular growth. The inactivation of tumor suppressors via epigenetic silencing or genetic alterations leads to misregulation of the cell cycle.⁴ Many patients with inherited cancer risk harbor a germline mutation (ie, an embryonic mutation present in all cells of the body) leading to the loss of a tumor suppressor gene. If a second mutation occurs in the remaining wild type allele (ie, the normally functioning second copy of the gene), or if the mutation creates a dominant negative (ie, nonfunctional competitor) protein, cell growth is uninhibited and can therefore drive tumor development. Examples of tumor suppressors that lead to cancer risk syndromes include *CDKN2A* (Fig 1) and *CDK4* (inherited melanoma; Fig 2). In the case of *CDKN2A*, the downstream products control the

transition between the growth (G_1) and synthesis (S) phases of the cell cycle, during which DNA replication occurs and a cell continues to grow and divide.

The third category of inherited genetic cancer risk factors is those involved in DNA repair and stability. Inactivation of these genes, such as *BRCA1* or *BRCA2*, increases the mutational rate of a cell and predisposes an individual to breast and other cancers.⁶ This article focuses on genetic syndromes that increase the risk of cutaneous MM, with mention of those that also increase ocular melanoma. The second article in this series focuses on genetic syndromes that increase the risk of nonmelanoma skin cancer.

MELANOMA-PREDOMINANT SYNDROMES**Key points**

- **Heredity melanoma is an autosomal dominant group of disorders**
- **Inherited mutations in *CDKN2A*, *CDK4*, *POT1*, and *TERT* confer a 60% to 90% lifetime risk of melanoma**
- **Testing criteria in areas of high melanoma incidence, such as Australia or the United States, include individuals with ≥ 3 primary MMs or a family history of ≥ 2 MMs or pancreatic cancer**
- **In areas of low/moderate incidence, such as the United Kingdom, testing is indicated in individuals with ≥ 2 primary melanomas or a family history of ≥ 3 MMs or pancreatic cancer**

Hereditary melanoma

Hereditary melanoma (also called familial atypical multiple mole syndrome) is an autosomal dominant group of disorders characterized by the presence of hundreds of dysplastic nevi and an increased risk of melanoma. Genetic alterations associated with hereditary melanoma syndrome include the tumor suppressors *CDKN2A* and *CDK4* and the telomerase complex proteins telomerase reverse transcriptase (*TERT*), and protection of telomeres 1 (*POT1*; Table I).

Epidemiology and evaluation. Familial clusters of melanoma have been identified worldwide.⁷ In individuals with a strong personal or family history of melanoma (ie, ≥ 3 individual melanomas in different blood relatives), the likelihood of finding a mutation associated with MM can be as high as 30% to 40%. In contrast, the likelihood of finding a germline mutation in families with a single melanoma is $\leq 1\%$.^{7–10} Unlike breast cancer, the young age of onset of melanoma is not considered a reliable criterion for

Table I. Summary of genetic syndromes associated with increased melanoma risk

Syndrome	Gene(s)	Locus	Inheritance	Melanoma	Clinical hallmarks	Other malignancies
Melanoma-predominant syndromes						
Hereditary melanoma	<i>CDK4</i>	12q14.1	AD	Cutaneous	Increased mole count and numerous dysplastic nevi	Nervous system tumors
	<i>CDKN2A</i>	9p21	AD	Cutaneous	Increased mole count and numerous dysplastic nevi	Pancreatic and nervous system
	<i>POT1</i>	9q31.33	AD	Cutaneous	Increased mole count and numerous dysplastic nevi	Gliomas
	<i>TERT</i>	5p15.33	AD	Cutaneous	Increased mole count and numerous dysplastic nevi	Ovarian, renal, bladder, breast, and lung
BAP1 cancer syndrome	<i>BAP1</i>	3p21.1	AD	Cutaneous and uveal	Melanocytic, pink or tan, dome-shaped nevi (epithelioid atypical Spitz tumors)	Renal and mesothelioma
Susceptibility to melanoma and renal cell carcinoma	<i>MITF</i>	3p14-p13	AD	Cutaneous	Increased nevus count and nonblue eye color	Renal
Melanoma-including syndromes						
Hereditary breast and ovarian cancer syndrome	<i>BRCA1</i> * and <i>BRCA2</i>	17q21.31 and 13q13.1	AD	Cutaneous and uveal (<i>BRCA2</i>)	N/A	Breast and ovarian
Li–Fraumeni syndrome	<i>TP53</i>	17p13.1	AD	Cutaneous and uveal [†]	N/A	Breast, bone and soft tissue, central nervous system, and leukemia
Xeroderma pigmentosum	<i>XPC</i> , <i>XPD</i> , and <i>XPA</i> [‡]	Various	AR	Cutaneous	Numerous lentigines at young age, freckling, keratitis, and iritis	Nonmelanoma skin cancer increased by 100-1000 fold
PTEN hamartoma tumor syndromes	<i>PTEN</i>	10q23.3	AD	Cutaneous	Trichilemmomas and multiple hamartomas	Breast, colorectal, thyroid, kidney, and endometrial

Syndromes associated with increased risk of either cutaneous or uveal melanoma. Hereditary melanoma, a group of high penetrance genes associated with a high risk of melanoma, was traditionally associated with just *CDKN2A* and *CDK4*. Recently, *POT1* and *TERT* have been added. The remaining genes represent other cancer syndromes that also increase the risk of melanoma. These syndromes also increase the risk of other cancers listed in the table. Testing for *CDKN2A* and other diseases can be identified through Gene Tests (<https://www.genetests.org/>).

AD, Autosomal dominant; AR, autosomal recessive; N/A, not applicable.

**BRCA1* less evidence of association with melanoma.

[†]*XPA* with less evidence of association with melanoma.

[‡]Degree of increase in MM risk associated with *TP53* mutations not well-established.

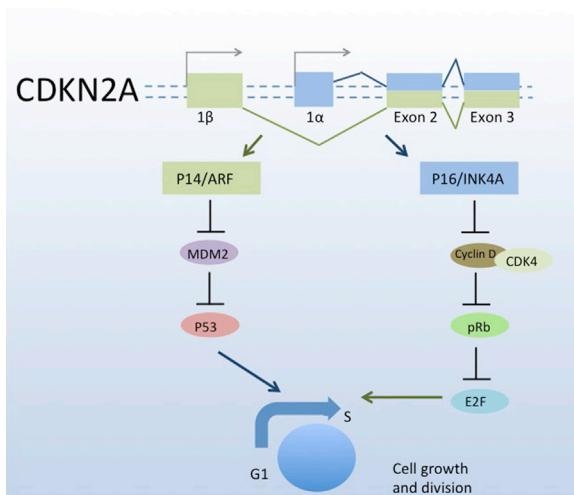


Fig 1. *CDKN2A* pathway. *CDKN2A* encodes 2 proteins that are translated from alternate reading frames: p16INK4A (P16), encoded by the alfa transcript, and p14ARF (P14), encoded by the beta transcript. Both P16 and P14 proteins are tumor suppressors important for cell cycle inhibition, specifically acting at the G₁ to S transition. Loss of such cell cycle suppressors allow cells with damaged DNA to proliferate and divide, leading to oncogenesis.

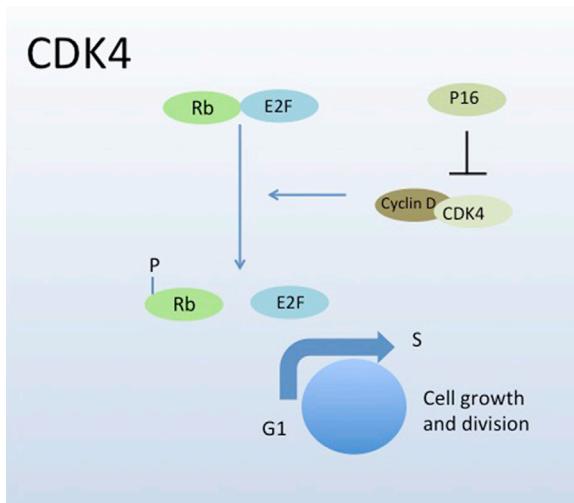


Fig 2. *CDK4* pathway. Mutations in *CDK4* change an arginine residue such that p16 can no longer bind. Subsequently, there is increased phosphorylation of retinoblastoma-bound E2F. Promotes the G₁ to S phase transition, promoting cell growth and proliferation.

genetic screening, although the average age of onset of melanoma in *CDKN2A* carriers is lower than that of noncarriers.^{11,12} *CDKN2A* is the most prevalent (ie, most commonly mutated) gene in patients with hereditary melanoma, present in around 40% of families, while the next most commonly mutated genes are those involved in telomere maintenance.



Fig 3. Atypical nevi. Photograph of a patient with numerous clinically atypical nevi. The skin examination revealed numerous tan to brown macules and papules scattered across the patient's back.

The latter mutations, including *POT1* and *TERT*, are prevalent in 9% of patients with hereditary melanoma and, when normally functioning, contribute to protection of exposed chromosomal ends.¹³

Cutaneous findings and cancer risk. Some patients with hereditary melanoma may also have numerous dysplastic nevi (Fig 3).¹⁴ On clinical skin examination, melanomas in these individuals are indistinguishable from sporadic melanomas, and should be evaluated based on traditional asymmetry, border, color, diameter, and evolution (ABCDE) criteria and on dermoscopic and histologic criteria.¹⁵ The clinical phenotype of individuals with hereditary melanoma is varied, and neither increased mole count nor the presence of dysplastic nevi are reliable criteria for selection of patients for genetic counseling or testing. Despite the large number of atypical nevi seen in carriers, the clinical phenotype is varied.

In areas with high levels of exposure to ultraviolet (UV) light, such as North America and Australia, the lifetime melanoma risk in carriers of the *CDKN2A* mutation who are in high-risk families is 76% and 91%, respectively, while that in areas of low levels of exposure to UV light (ie, the United Kingdom) is lower (58%).¹⁶ Lifetime risk estimates for *CDK4*, *POT*, *TERT*, and other high-risk melanoma genes have not yet been established.

Genetics. *CDKN2A* encodes 2 proteins that are created by alternative transcription of the same DNA sequence. This is done by starting at 2 different places within the DNA sequence, leading to transcription in different reading frames, resulting in 2 different proteins: p16INK4A (p16) and p14ARF

(p14; Fig 1) of exon 1.^{17,18} Both the *CDKN2A*/p16 and *CDKN2A*/p14 proteins are tumor suppressors, but they have completely different functions. *CDKN2A*/p16 regulates function of the retinoblastoma pathway. *CDKN2A*/p14 regulates function of the p53 pathway. Depending on the site of the mutation, a mutation in *CDKN2A* can impact the function of *CDKN2A*/p16 or *CDKN2A*/p14—or both proteins, if the mutation is located in an area of overlap between the 2 gene products.¹⁹⁻²² Members of some families with mutations in *CDKN2A*/p16 have up to a 20% risk for pancreatic cancer.^{23,24} Individuals with mutations affecting *CDKN2A*/p14 are at increased risk for central nervous system tumors.^{3,7,25} Because of recent findings of p14 mutations in association with astrocytoma, some now consider this to be a distinct clinical entity (melanoma-astrocytoma syndrome).²⁶

Mutations in *CDK4* are far more rare than those in *CDKN2A*, and have been identified in approximately 20 melanoma families. All mutations seen thus far occur in a single codon (codon 24) at 2 sites (p.R24C or p.R24H).^{27,28} These mutations disrupt the binding site of p16 and lead to dysregulation of the cell cycle (Fig 2).²⁹

Mutations in telomere-related genes, such as *POT1*, shelterin complex genes, and *TERT* have also been identified in classic-appearing hereditary melanoma families. *POT1* founder mutations were identified in families with clusters of cutaneous MM in Italy.^{30,31} *POT1* encodes part of a telomere-protecting complex (shelterin), which helps to protect chromosomal ends from damage, degradation, or inappropriate processing by DNA repair mechanisms.³² Mutations in other shelterin-complex components—adrenocortical dysplasia homologue (*ACD*) and telomeric repeat binding factor 2, interacting protein (*TERF2IP*)—were also recently identified in association with familial cutaneous MM. Overall, mutations in these shelterin complex genes (ie, *ACD*, *TERF2IP*, and *POT1*) are found in 9% of MM families that do not have *CDKN2A* or *CDK4* mutations.¹³ In addition, the *TERT* was found to be mutated at the promoter start site in melanoma families without *CDKN2A* or *CDK4* mutations.^{33,34} These mutations create new binding sites for *TERT*, increasing transcription.³⁵ Increased *TERT* activity may allow unlimited cell division and subsequently promote cancer progression.³⁵

Management. There are currently no specific guidelines for genetic testing for hereditary melanoma. Recently, genetic counseling and testing criteria for *CDKN2A* mutations were developed. These criteria vary by geographic melanoma incidence. In areas of moderate to high MM

Table II. Current testing recommendations for *CDKN2A* mutations*

	No. of primary CMMs	Family history
Low melanoma incidence area (United Kingdom)	≥2	2 relatives [†] with melanoma or 1 with melanoma and 1 with pancreatic cancer
Moderate to high incidence melanoma area (US and Australia)	≥3	3 melanomas or 2 melanomas and 1 pancreatic cancer or 1 melanoma and 2 pancreatic cancers

CMM, Cutaneous malignant melanoma.

*Adapted from Leachman et al.⁸

[†]Either first- or second-degree relative.

incidence (ie, the southern United States and Australia), testing for *CDKN2A* mutations is indicated in individuals with ≥3 primary invasive melanomas. In areas of moderate to high incidence, testing is also indicated in individuals who have 3 first- or second-degree relatives with diagnoses of melanoma or pancreatic cancer. In areas of low melanoma incidence, testing is indicated in individuals with ≥2 primary invasive melanomas or those who have 2 relatives with melanoma or pancreatic cancer (Table II).^{2,8}

However, the availability of new panels that include multiple melanoma risk genes complicate this decision-making process, and dermatologists should be attuned to updated guidelines as they emerge. It is prudent to begin with the most common risk genes (ie, *CDKN2A*) and proceed to test for other more rare variants with prioritization by the rest of the family cancer history or to consider panel testing.

If a high-risk mutation is found, based on current consensus guidelines, patients with known *CDKN2A*/p16 mutations are candidates for annual pancreatic cancer screening via endoscopic ultrasonography or magnetic resonance cholangio-pancreatography—although the age at which to begin screening has not been reached via consensus at this time.^{23,36} Regular follow-up with gastroenterology will assist with optimization of screening.

The National Comprehensive Cancer Network (NCCN) guidelines recommend that individuals with a personal history of MM or *CDKN2A* mutation carriers, regardless of MM history, undergo a yearly skin examination, and recommends that patients are educated on skin cancer prevention (ie, sunscreen use and sun avoidance) and self-skin examination. The NCCN also notes that those at higher risk because of a personal history (ie, multiple primaries

or early onset), multiple atypical moles or dysplastic nevi, increased UV exposure, or other environmental risk factors may require more frequent clinical examinations.³⁷ The NCCN does not have standard recommendations for genetic testing beyond recommending genetic counseling for those with a strong family history of MM. Individuals who know they carry a high-risk variant are more likely to engage in preventive behaviors.³⁸

Negative genetic testing. The stringent selection of families for genetic testing can yield a high positive mutation rate, but not all individuals with high-risk features or a family history will carry a known genetic variant. If no mutation is found in a patient in the setting of other mutation-carrying family members, the patient's risk of melanoma is still around twice that of the general population.³⁹

If a mutation is not identified in a patient or in other family members who are tested, the patient may either have an extremely elevated risk because of an as-yet unidentified high-risk variant or it is possible that no single mutation is contributing a large amount of risk.³⁹ Only about 40% of melanoma-prone families have an identifiable *CDKN2A* mutation, and based on currently available genetic data, approximately 10% are caused by other risk genes (eg, *POT* and *TERT*). This means that approximately 50% of hereditary melanomas are caused by mutations in genes we have not yet uncovered; it is therefore possible that genetic testing will yield no known mutation, even in families that are considered high-risk from a clinical perspective.¹⁷ This could be because of other uncommon, yet to be identified high-risk genes or a combination of effects of low- or moderate-risk genes with superimposed environmental risk(s).

Overall, individuals with a strong family history of MM—regardless of whether a mutation is found through individual gene sequencing or panel testing—still have an increased risk of melanoma compared to the general population. Therefore, such individuals should still undergo at minimum yearly total body skin examinations and adhere to sun protective measures. In addition, as our understanding of melanoma genetics and risk genes evolves, patients should be periodically reevaluated to see whether they are appropriate candidates for genetic testing.

BAP1 cancer syndrome

BAP1 (BRCA1 associated protein-1/ubiquitin carboxy-terminal hydrolase) cancer syndrome is a rare genetic syndrome characterized by the development of uveal melanomas, mesotheliomas and,



Fig 4. Melanocytic *BAP1*-mutated atypical intradermal tumors. These are the classic pink, dome-shaped tumors that occur in nearly all individuals with *BAP1* cancer syndrome. (Courtesy of Dr Carbone.)

less frequently, cutaneous melanomas, various types of carcinomas—mostly from the kidney and gallbladder—sarcomas, and brain tumors.⁴⁰⁻⁴⁴ By 55 years of age, all carriers of germline *BAP1* mutations have developed at least 1, and often multiple, malignancies.⁴⁵

Melanocytic *BAP1*-mutated atypical intradermal tumors (MBAITs) occur in most individuals with *BAP1* cancer syndrome.⁴⁶ These are raised, melanocytic, pink or tan, dome-shaped, benign lesions (Fig 4).⁴⁶ These “melanocytic tumors” have been referred to in the literature as atypical Spitz tumors (ASTs) because they histologically resemble Spitz nevi and melanoma, having large melanocytes with superficial and deep mitotic activity (Fig 5).^{44,47} However, additional studies have revealed that the histologic and molecular characteristics of these lesions are different from Spitz tumors and ASTs. Molecularly, MBAITs are characterized by *BAP1* inactivation (and are sometimes called “Bapomas”) and often *BRAF* mutation, which is common in melanoma.⁴⁸ These lesions do not often progress to malignant tumors, but they should prompt genetic testing for *BAP1* germline mutations.⁴⁶

Epidemiology and evaluation. To date, there have not been large epidemiologic studies of *BAP1* germline mutations and association with cutaneous or uveal MM.⁴⁹ Recently, a study of a population-based sample reported that an estimated 0.63% of melanoma probands carried *BAP1* mutations.⁵⁰ About 67% of carriers of germline *BAP1* mutations have 1 and often multiple MBAITs because their number increases with age, and about 12% of them developed cutaneous melanomas.⁴⁶ The presence of mesothelioma and uveal MM in a family is the most

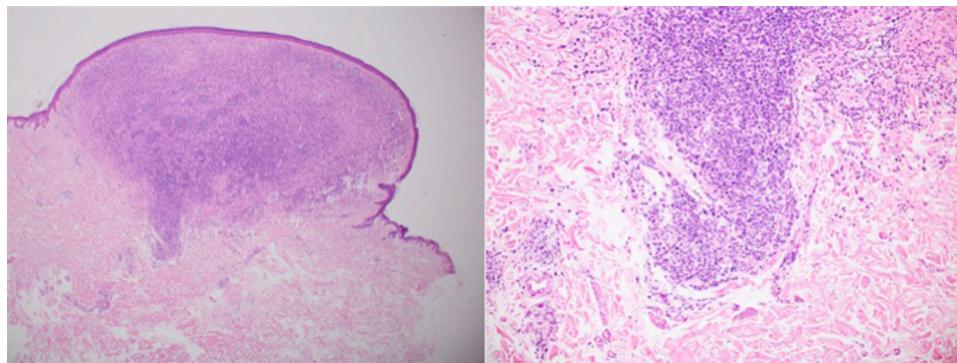


Fig 5. Hematoxylin–eosin-stained slide of melanocytic *BAP1*-mutated atypical intradermal tumors (original magnifications, $\times 20$ and $\times 100$). There are large melanocytes with superficial and deep mitotic activity. (Courtesy of Dr Carbone.)

characteristic feature of the *BAP1* cancer syndrome.^{45,46,51}

Genetics. *BAP1* is a tumor suppressor that is part of the ubiquitin c-terminal hydrolase family of deubiquitylating enzymes that has role in DNA damage repair. Both mesotheliomas and melanomas are associated with exposure to environmental carcinogens— asbestos for mesothelioma and sunlight for melanomas. Recent studies found that germline *BAP1* mutations significantly lower the threshold amount of asbestos required to induce mesotheliomas in mice.⁵² Similarly, it is possible that *BAP1* mutations increase susceptibility to UV light carcinogenesis, which would explain the high incidence of melanomas in these families.

Evaluation and management. Current guidelines have not yet formalized criteria for *BAP1* screening, but in families with mesothelioma, benign melanocytic neoplasms at a young age, and cutaneous or uveal melanoma, genetic testing may be useful to identify *BAP1* mutation carriers. Individuals with *BAP1* mutations should be screened at least annually for uveal melanoma and mesothelioma, in addition to cutaneous melanoma, and well as self-skin examinations and photoprotection.⁴⁶

Susceptibility to melanoma and renal cell carcinoma

Germline mutations in microphthalmia-associated transcription factor (MITF) are associated with increased MM risk, increased nevus count, nonblue eye color, and renal cell carcinoma.^{53,54} Based on estimates of the burden of MITF mutations in the general white population, approximately 1% of all melanomas are estimated to be caused by MITF mutations.⁹ MITF mutations were found to significantly increase MM risk in 3 studies, with odds ratios ranging from 1.7 (95% confidence interval [CI], 1.1-2.7)⁵⁴ to 2.2 (95% CI, 1.41-3.45)⁵⁵ and up to

4.78 (95% CI, 2.05-11.75).⁵³ MITF variants may enable melanocyte migration and invasion and therefore increase MM risk.⁴⁹ Given the variability in the degree to which different MITF mutations increase MM risk, routine genetic testing is not currently standard practice.⁵⁶ However, as panel testing evolves, MITF is becoming more routinely incorporated.

MELANOMA-INCLUDING SYNDROMES

Key points

- Individuals with mutations in *BRCA1* or *BRCA2* have an increased risk of breast, ovarian, prostate, and pancreatic cancer, and up to a 2-fold increased risk of melanoma
- Individuals with mutations in *P53* (Li–Fraumeni syndrome) may be at increased risk of melanoma
- Mutations in UV repair genes that cause *xeroderma pigmentosum* cause extreme photosensitivity and increase melanoma risk up to 1000-fold

Hereditary breast and ovarian cancer syndrome

Individuals with mutations in *BRCA1* or *BRCA2* have an increased risk of breast, ovarian, prostate, and pancreatic cancer. The degree to which *BRCA* mutation carriers are at increased risk of cutaneous and uveal melanoma has not been well characterized.^{56–58} In addition, the overlap in phenotype with *CDKN2A* carriers with respect to both melanoma and pancreatic cancer risk makes a careful family history and genetic test selection, if indicated, extremely important. The breast cancer linkage consortium reported a relative risk of MM of 2.6 in *BRCA2* carriers.⁵⁹ Data on *BRCA1* and MM are sparser. One large recent prospective study reported a trend in *BRCA1* mutation carriers toward increased MM risk

(standardized incidence ratio, 3.31; $P = .004$).⁶⁰ In addition, melanoma and breast cancer have been reported to co-occur in numerous pedigrees.⁶¹

BRCA1 and *BRCA2* are DNA repair-involved genes that accumulate near DNA strand breaks. Mutations in *BRCA1* or *BRCA2* decrease ability to repair DNA damage, leading to increased susceptibility to DNA mutagens, particularly those that cause double-stranded breaks.^{62,63}

Current recommendations for MM screening for *BRCA* carriers include annual clinical examinations of the skin and eyes.⁵⁶ Other prophylactic measures and cancer surveillance recommendations for *BRCA* mutation carriers is not included in the present article but can be found within the NCCN guidelines (http://www.nccn.org/laneproxy.stanford.edu/professionals/physician_gls/f_guidelines.asp), which are accessible free of charge.

Li–Fraumeni syndrome

Li–Fraumeni syndrome (LFS) is an autosomal dominant cancer syndrome defined clinically by early onset soft tissue and bone sarcomas, leukemia, breast cancer, nervous system tumors, often occurring before age 30. Germline mutations in *TP53* are present in most LFS families.⁶⁴ More recently, case reports of multiple cutaneous MM or clustering of MM in LFS families have been reported.^{65–67} *TP53* is a tumor suppressor involved in ensuring genome integrity and disruption of its activity allows unchecked progression through the cell cycle and increased genome instability. NCCN guidelines recommend yearly skin examination in LFS patients, along with self-skin exam and photoprotection.⁶⁸ Mutation carriers with a history of radiation have a particularly increased risk of cutaneous malignancy, and the risks and benefits should be considered before performing any radiographic studies.

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) refers to a spectrum of autosomal recessive diseases caused by mutations in DNA repair genes (*XPA*–*XPG*) that encode proteins that repair UV-induced DNA damage (nucleotide excision repair [NER]).

Cutaneous findings. Patients with XP have extreme photosensitivity and freckling (at 1–2 years of age), a predisposition to the development of keratitis, iritis, and choroid melanoma, and basal cell carcinoma, squamous cell carcinoma, and MM at an early age. Other noncutaneous findings include hyporeflexia or areflexia, deafness, and intellectual disability.⁶⁹

Epidemiology and evaluation. Individuals with XP have an estimated 600- to 8000-fold

increased risk of MM. The median age of skin cancer diagnosis is 8 years. The lifetime risk of MM in patients with XP ranges from 5% to 20%. The incidence of XP is only 1 in 250,000 live births.⁷⁰ These patients have an estimated 10,000-fold increased risk of nonmelanoma skin cancer by 20 years of age.⁷¹

Genetics. NER normally functions to remove UV radiation–induced pyrimidine dimers. Patients with XP have mutations in the many genes that encode NER proteins (XP group A, B, C, D, E, F, and G) and have an impaired ability to repair UV-damaged DNA.⁷² The *XPC* and *XPE* genes help recognize DNA damage; *XPA* helps to verify this damage. *XPB* and *XPD* encode helicases that unwind DNA, while *XPF* and *XPG* nucleases help cut out the UV-damaged DNA. In the absence of normally functioning NER proteins, XP patients are exceedingly sensitive to the carcinogenic effects of UV radiation. Of all of the NER genes, mutations in *XPC* and *XPD* have the strongest association with increased MM risk.⁷³

Evaluation and management. The diagnosis of XP is often made clinically, for example, because of the presence of lentigines at a young age. Patients and families must be counseled regarding UV protection to an extreme degree, such as covering windows at home, in cars, and at school, and even some hospital or fluorescent lights that emit UV radiation. Patients should cover skin when outdoors during daylight, with sunscreen, long pants, long sleeves, and gloves. Regular dermatologic follow-up for skin examination is essential, along with an eye examination by an ophthalmologist. Because of the degree of photoprotection required, these patients are likely to be vitamin D–deficient, and supplementation should be prescribed.^{71,74} There are many support groups available to XP patients and their families, such as Camp Sundown (<http://www.xps.org/>) or XP Family Support (<http://www.xpfamilysupport.org/>). Physicians should also consider referral of these patients to the National Institutes of Health (<http://www.cc.nih.gov/referpatients/>).

Phosphatase and tensin homolog hamartoma tumor syndromes

Germline mutations in phosphatase and tensin homolog (*PTEN*), a tumor suppressor gene, lead to a group of clinical syndromes in the umbrella category of *PTEN* hamartoma tumor syndromes. These syndromes include Cowden syndrome, which presents in adulthood, and Bannayan-Riley-Ruvalcaba syndrome, which presents in children.⁷⁵

A recent large study of individuals with genetically proven Cowden syndrome found an increased risk of numerous cancers, including melanoma (standardized incidence ratio, 8.5 [95% CI, 4.1-15.6]) and breast, thyroid, endometrial, kidney, and colorectal cancer.⁷⁶ Other studies have also found an even greater magnitude of increased melanoma risk (standardized incidence ratio, 28.3 [95% CI, 7.6-35.4]). Interestingly, women with Cowden syndrome had a 2-fold higher overall risk of cancer than men with Cowden syndrome.⁷⁷

Because individuals with Cowden syndrome are at high risk for numerous cancers, including melanoma, they should be aggressively screened with annual skin examinations.

Modifiers of other high-risk melanoma genes

MC1R. *MCR1* (melanocortin 1 receptor) variants increase MM risk in part by altering skin pigmentation. Genetic alterations in *MC1R* can lead to red hair and fair skin.^{78,79} *MC1R* is a transmembrane protein of the G protein-coupled receptor family. *MC1R* encodes the G protein-coupled melanocortin 1 receptor, which, when activated by alfa-melanocyte-stimulating hormone, leads to increase in intracellular cyclic adenosine monophosphate, ultimately increasing production of eumelanin versus pheomelanins (red/yellow). Increased eumelanin leads to darker skin pigmentation, which protects against UV radiation, whereas pheomelanins sensitize to UV damage through the formation of free radicals.⁷⁹ Interestingly, *MC1R* variants also increase MM risk even after adjusting for hair color and ability to tan.^{80,81} This has been confirmed molecularly; cells containing *MC1R* mutations have defects in their ability to handle oxidative stress and reduced ability to handle DNA repair.^{82,83}

While *MC1R* variants are independent MM risk factors, it also seems that *MC1R* variants can modify melanoma risk-associated *CDKN2A* mutations.

Individuals with both *CDKN2A* variants and *MC1R* variants have 2 to 4 times the MM risk and earlier age of MM (by about 10 years compared to noncarriers) and increased likelihood of multiple primary MM compared to those with *CDKN2A* without *MC1R* variants.^{84,85} A metaanalysis identified a dose effect for some *MC1R* variants in which *CDKN2A* carriers with a single *MC1R* variant had twice the MM risk compared to *CDKN2A* carriers with no *MC1R* variants. In addition, *CDKN2A* carriers with multiple *MC1R* variants had 4 times the MM risk compared to noncarriers.⁸⁵

Routine clinical testing for *MC1R* variants is not currently recommended. However, those with fair pigmentation, freckling, or red hair should be

counseled about chemoprevention through aggressive photoprotection and annual screening skin examinations. *MC1R* is not part of the spectrum of mutations that cause hereditary melanoma, but is discussed here as a known genetic variant that increases MM risk and to remind clinicians that known MM risk factors, such as pigmentation, increase the degree of risk in hereditary melanoma mutation carriers.

In conclusion, dermatologists are often the front-line providers involved in identifying individuals at high risk of melanoma because of inherited traits. Proper identification of these individuals is imperative, because it significantly informs their skin cancer risk, risk of internal cancers, and enables targeted screening and prevention. In addition, family members of these individuals should be screened clinically and with genetic testing when indicated. Genetic testing has been adopted as part of routine clinical practice for patients with breast, ovarian, and colon cancers and a growing list of other primary cancers. However, MM patients are not routinely tested for *CDKN2A* or other mutations. Both physicians and patients are increasingly aware of the utility and availability of genetic testing. At the time of publication of this article, there are 14 single-gene or panel based commercial tests presently available for *CDKN2A* testing in the United States⁸⁶ and 11 for *CDK4*.⁸⁷ For the most up to date list, visit www.genetests.org for reliable and up to date genetic testing options.

Individuals with a suggestive history should be referred for additional evaluation to a dermatologist with expertise in genetics, a genetic counselor, or a medical geneticist. A family pedigree should be established so that high-risk family members can also consider screening. Regardless of whether a case is associated with an identifiable inherited mutation, epidemiologic studies have found that individuals with melanoma (and their blood relatives) are at increased risk of numerous cancers, including nonmelanoma skin cancer, prostate, breast, bone, and colon cancers, non-Hodgkin lymphoma, and multiple myeloma.⁸⁸ Therefore, it is important to counsel patients with melanoma about risk of other cancers and consider genetic counseling and genetic panel testing.

Patients and physicians should be aware that all high-risk patients require close follow-up, regardless of whether or not a mutation is found. Strict surveillance, digital total body photography, and dermoscopy are among techniques that may contribute to a high rate of detection of early MM (ie, a lower Breslow depth) in high-risk patients.^{89,90}

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Familial skin cancer syndromes

Increased risk of nonmelanotic skin cancers and extracutaneous tumors

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Learning objectives

After completing this learning activity, participants should be able to explain how to screen patients for inherited nonmelanoma skin cancer risk; discuss new developments in next generation sequencing and new approaches for genetic testing of patients with nonmelanoma skin cancer; and develop an appropriate management plan for a patient with nonmelanoma skin cancer.

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Nonmelanoma skin cancers (NMSCs) represent the most common malignancies worldwide, with reported incidence rising each year. Both cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC), as well as other NMSCs, represent complex diseases with a combination of environmental and genetic risk factors. In general, hereditary cancer syndromes that increase the risk of NMSC fall under several broad categories: those associated with immunodeficiencies, those that affect skin pigmentation, and those that perturb key molecular pathways involved in the pathogenesis of NMSCs. Many of the syndromes are also associated with extracutaneous manifestations, including internal malignancies; therefore, most require a multidisciplinary management approach with a medical geneticist. Finally, dermatologists play a critical role in the diagnosis and management of these conditions, because cutaneous findings are often the presenting manifestations of disease. (J Am Acad Dermatol 2016;74:437-51.)

Key words: Bloom syndrome; dyskeratosis congenita; genetic testing; Gorlin syndrome; Muir-Torre syndrome; nonmelanoma skin cancer; oculocutaneous albinism; Rothmund-Thomson syndrome; Werner syndrome.

INTRODUCTION

Nonmelanoma skin cancers (NMSCs) represent the most common malignancies in the United States, making up 96% of all skin cancers and accounting for 2 to 3 million cases each year.¹ Like melanoma,

cutaneous squamous cell carcinoma (SCC) and basal cell carcinoma (BCC) represent complex diseases influenced by both the external environment and inherent genetics. While tumor development in both often occurs sporadically and is strongly associated

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Abbreviations used:

5-FU:	5-fluorouracil
ADA1:	adenosine deaminase 1
ADA-SCID:	adenosine deaminase severe combined immunodeficiency
BCC:	basal cell carcinoma
BCNS:	basal cell nevus syndrome
BDCS:	Bazex-Dupré-Christol syndrome
BLM/RECQL3:	Bloom syndrome, RecQ helicase-like
C10Orf11:	chromosome 10 open reading frame 11
C16Orf57:	chromosome 16 open reading frame 57
DFSP:	dermatofibrosarcoma protuberans
DC:	dyskeratosis congenita
EV:	epidermolytic hyperplasia
EVER1:	epidermolytic hyperplasia 1
EVER2:	epidermolytic hyperplasia 2
HNPPC:	hereditary nonpolyposis colon cancer
HPV:	human papillomavirus
IHC:	immunohistochemistry
MSI:	microsatellite instability
MMR:	mismatch repair
MTS:	Muir-Torre syndrome
MSSE:	multiple self-healing squamous epithelioma
MLH1:	MutL homolog 1
MSH2:	MutS homolog 2
MSH6:	MutS homolog 6
NK:	natural killer
NMSC:	nonmelanoma skin cancer
OCA:	oculocutaneous albinism
OCA2:	oculocutaneous albinism 2
PTCH1:	patched1
PTCH2:	patched2
PMS2:	postmeiotic segregation increased 2
RECQL4:	RecQ protein-like 4
RTS:	Rothmund-Thomson syndrome
SMO:	smoothened
SLC24A5:	solute carrier family 24, member 5
SLC45A2:	solute carrier family 45, member 2
SHH:	sonic hedgehog
SCC:	squamous cell carcinoma
SUFU:	suppressor of fused gene
TGFBR1:	transforming growth factor beta receptor 1
TYR:	tyrosinase
TYRP1:	tyrosinase-related protein 1
UVR:	ultraviolet radiation
WRN/RECQL2:	Werner syndrome, RecQ helicase-like
XP:	xeroderma pigmentosum

with risk factors such as ultraviolet radiation, immunosuppression, viral infections, and radiotherapy, there is a subset of cases in which it occurs in the context of hereditary cancer syndromes. In general, these genetic syndromes fall under several broad categories: those associated with immunodeficiency, those that affect pigmentation, and those that perturb key molecular pathways involved in the pathogenesis of NMSCs. This article is an overview of the clinical features, epidemiology, evaluation, genetics, and management of the major

hereditary genodermatoses with NMSC predisposition (Table 1). While the risk of NMSC is increased in many hereditary conditions associated with immunodeficiency, this article focuses on those with the most direct risk of skin cancer.

FAMILIAL CANCER SYNDROMES AND NONMELANOMA SKIN CANCER RISK: INCREASED RISK OF BASAL CELL CARCINOMA

Key points

- **Basal cell nevus syndrome is an autosomal dominant syndrome driven by aberrant activation of the sonic hedgehog pathway; it is characterized by developmental defects and multiple neoplasms, including the development of numerous basal cell carcinomas**
- **Developmental defects in patients with basal cell nevus syndrome include palmar and plantar pits, craniofacial anomalies, corpus colossum dysgenesis, falx cerebri calcification, coarse facies, cleft palate, and spina bifida occulta**
- **Extracutaneous neoplasms in patients with basal cell nevus syndrome include medulloblastomas, rhabdomyosarcomas, odontogenic keratocysts, fibrosarcomas, meningiomas, cardiac fibromas, and ovarian fibromas**
- **Bazex-Dupré-Christol syndrome and Rombo syndrome are rare genetic disorders that have a high degree of phenotypic overlap and are associated with increased risk of basal cell carcinoma**

Basal cell nevus syndrome (Gorlin syndrome, Gorlin-Goltz syndrome, and nevoid basal cell carcinoma)

Basal cell nevus syndrome (BCNS) is an autosomal dominant disorder characterized by the development of multiple neoplasms (including BCCs, medulloblastomas, rhabdomyosarcomas, odontogenic keratocysts, fibrosarcomas, meningiomas, cardiac fibromas, and ovarian fibromas) and developmental defects (including palmar and plantar pits, craniofacial anomalies [eg, macrocephaly and frontal bossing], corpus colossum dysgenesis, falx cerebri calcification, coarse facies, cleft palate, bifid ribs, and spina bifida occulta).²⁻⁷

Cutaneous findings. The hallmark of BCNS is the development of multiple BCCs; although some patients develop >1000 BCCs over their lifetimes and rare patients fail to develop any, the median number in affected individuals is 8. BCCs can appear as early as the first year of life and develop

by a median age of 20 years (Fig 1).^{5,6} Histologically, they are indistinguishable from sporadic BCCs; clinically, they typically resemble sporadic tumors and are found on both sun-exposed and nonexposed skin.^{5,7} However, because they can occasionally resemble vascular lesions or be pedunculated, especially around the neck, the finding of multiple acrochordon-like lesions in pediatric patients should raise suspicion for BCNS and may warrant obtaining a biopsy specimen. Secondary signs, such as ulceration, crusting, and bleeding, rarely occur before adolescence. Many lesions grow slowly or remain static after reaching a certain size; however, they may become aggressive after adolescence and occasionally metastasize.⁷ Milia and epidermal cysts are reported in about 50% of cases.^{6,7}

Epidemiology and evaluation. BCNS has a prevalence of 1 per 40,000 to 57,000 individuals.^{8,9} Race influences both the incidence and penetrance of BCNS, with only about 5% of cases involving African Americans and Asians.^{10,11} In addition, while approximately 80% to 90% of affected white patients develop multiple BCCs over their lifetimes, <15% of patients with darker skin have >2 BCCs; as a result, most are diagnosed by the incidental discovery of asymptomatic odontogenic keratocysts during dental work or facial radiographic examination.^{4,5} The diagnosis of BCNS is supported by the finding of either 2 major or 1 major and 2 minor clinical criteria (Table II).¹² The following studies should be considered to aid in the diagnosis of individuals with suspected BCNS: a radiograph or computed tomography scan of the skull to show calcified falx cerebri, panoramic films/magnetic resonance imaging scans to identify odontogenic cysts, a chest radiograph to document rib abnormalities, and hand and foot radiographs that can reveal lytic bone lesions.^{5,13} However, this should be weighed against the harms of exposing true cases to unnecessary ionizing radiation and increasing their already elevated risk for BCC development. In questionable situations, genetic testing can be used for corroboration and the diagnosis of BCNS can be made with just 1 major criterion in the presence of molecular confirmation.¹⁴ A consensus statement from 2011 recommended genetic testing for the tumor suppressor Patched 1 (*PTCH1*) in the following scenarios: (1) prenatal testing if there is a known familial mutation; (2) confirmatory diagnosis in patients not meeting sufficient clinical diagnostic criteria; and (3) predictive testing for patients with affected family members who are at risk but do not meet clinical criteria.¹⁴

Genetics. In 1996, germline mutations in *PTCH1* on chromosome 9q22-31 were identified as the primary cause of BCNS. *PTCH1* encodes a transmembrane glycoprotein that is a member of the sonic hedgehog (SHH) pathway, the primary driver of BCC pathogenesis (Fig 2).¹⁵ Inactivating mutations in *PTCH1* lead to aberrant upregulation of SHH signaling and increased cell growth. Loss of heterozygosity at the *PTCH1* site by a “second hit” underlies the development of multiple BCCs in patients with BCNS. Genetic analysis has identified *PTCH1* alterations in 40% to 85% of patients with BCNS, the majority of which cause premature truncation of the protein.^{16,17} Although penetrance is near complete, phenotypic expression is variable and is not correlated to the type of *PTCH1* mutation.¹⁸

More recently, germline loss of function mutations in the suppressor of fused gene (*SUFU*) on chromosome 10q24.32 have also been detected in families meeting diagnostic criteria for BCNS.¹⁹ *SUFU* is a member of the SHH pathway downstream from *PTCH1* and is also involved in medulloblastoma.²⁰ In addition, several cases of BCNS have been reported to have been caused by mutations in *PTCH2* on chromosome 1p32.²¹ Approximately 20% to 30% of BCNS cases are de novo, with neither parent carrying the genetic mutation.²²

Management. The management of patients with BCNS requires both surveillance for the development of syndrome-related complications (Table III) and treatment of postnatal tumors and odontogenic keratocysts. Pediatric patients should be followed by a medical geneticist annually to ensure that all multidisciplinary screening issues are addressed and referrals to appropriate specialists are made.¹⁴

Treatment of BCCs in BCNS can be extremely difficult because of the preponderance of tumors. As in cases of sporadic BCC, excision as well as electrodesiccation and curettage are often used; however, because of concerns of disfigurement and discomfort from multiple surgical procedures, CO₂ laser therapy in combination with Mohs micrographic surgery can be an option in select patients.²³ In addition, superficial BCCs can be managed by topical 5% 5-fluorouracil (5-FU), topical imiquimod, or photodynamic therapy.²⁴⁻²⁷ A placebo controlled phase III randomized trial has also found that vismodegib, a smoothed (*SMO*) antagonist and SHH pathway inhibitor, can reduce the tumor burden in patients with BCNS.²⁸ This treatment is complicated by high rates of adverse effects and tumor regrowth after discontinuation.

Table I. Summary of select genetic conditions associated with an increased risk of nonmelanoma skin cancer

Condition	Gene	Locus	Function	Pattern of transmission	Commercial tests
Increased risk of basal cell carcinoma					
Basal cell nevus syndrome	<i>PTCH1</i> , <i>PTCH2</i> , and <i>SUFU</i>	9q22.32, 1p34.1, and 10q24.32	Hedgehog signaling pathway members	AD	Ambry Genetics, Prevention Genetics, Fulgent Diagnostics, Invitae, Emory Genetics
Bazex-Dupré-Christol syndrome	Unknown	Xq25-27.1	DNA repair and regulation of cell cycle	XLD	
Rombo syndrome	Unknown	Unknown		AD	
Increased risk of squamous cell carcinoma					
Xeroderma pigmentosum	<i>XPA</i> - <i>XPG</i> and <i>XPV</i>	9q22.33, 2q14.3, 3p25.1, 19q13.32, 11p11.2, 16p13.12, 13q33.1, and 6p21.1	Nucleotide excision repair	AR	Fulgent Diagnostics and Prevention Genetics
Multiple self-healing squamous epithelioma	<i>TGFBR1</i>	9q22.33	TGF-β signal transduction	AD	Ambry Genetics, Fulgent Diagnostics, Prevention Genetics, Gene Dx, and Emory Genetics
Oculocutaneous albinism (OCA1-OCA7)	<i>TYR</i> , <i>OCA2</i> , <i>TYRP1</i> , <i>SLC45A2</i> , unidentified, <i>SLC24A5</i> , and <i>C10Orf11</i>	11q14.3, 15q12-q13, 9p23, 5p13.2, 4q24, 15q21.1, 10q22.2-22.3	Melanin synthesis	AR	Fulgent Diagnostics, Prevention Genetics, Baylor Genetics Labs, ARUP Laboratories, Emory Genetics, and Courtagen Diagnostics
Epidermolytic hyperkeratosis	<i>EVER1</i> and <i>EVER2</i>	17q25.3, 17q25.3	Signal transduction in endoplasmic reticulum	AR, AD	Fulgent Diagnostics
Dyskeratosis congenita	<i>DKC1</i> , <i>TERC</i> and <i>TINF2</i> , <i>TERT</i> and <i>RTEL1</i> , <i>NHP2</i> , <i>NOP10</i> , <i>WRAP53</i> , <i>CTC1</i> , and <i>ACD</i>	Xq28, 3q26.2 and 14q12, 5p15.33 and 20q13.33, 5q35.3, 15q14, 17p13.1, 17p13.1, and 16q22.1	Telomere maintenance and trafficking	XLR AD AR and AD AR	Ambry Genetics, Fulgent Diagnostics, Prevention Genetics, Molecular Genetics Laboratory Cincinnati Children's Hospital Medical Center, Emory Genetics, and ARUP Laboratories
Huriez syndrome	Unknown	4q23	Unknown	AD	
Rothmund-Thomson syndrome	<i>RECQL4</i> and <i>C16Orf57</i>	8q24.3, 16q13	Chromosomal stability, telomere maintenance and trafficking	AR	Fulgent Diagnostics, Prevention Genetics, Emory Genetics, etc
Bloom syndrome	<i>BLM</i> / <i>RECQL3</i>	15q26.1	Chromosomal stability	AR	Centogene AG-The Rare Disease Company

Werner syndrome	WRN/RECQL2	8p12	Chromosomal stability	AR	Fulgent Diagnostics, Prevention Genetics, etc
Increased risk of soft tissue/other NMSCs ADA-SCID	ADA1	20q13.11	Purine metabolism	AR	Purine Metabolic and Immunodeficiency Lab
Muir-Torre syndrome	MLH1, MSH2, MSH6, and PMS2	3p22.2, 2p21, 2p16.3, 7p22.1	Mismatch repair	AD	Ambry Genetics, Fulgent Diagnostics, etc

For each condition, the genetic defect and locus, gene function, pattern of transmission, and names of commercial testing facilities are provided.
AD, Autosomal dominant; ADA-SCID, adenosine deaminase severe combined immunodeficiency; AR, autosomal recessive; NMSC, nonmelanoma skin cancer; TGF- β , transforming growth factor-beta; XLD, X-linked dominant; XLR, X-linked recessive.



Fig 1. Basal cell nevus syndrome. Clinical photograph depicting the multiple basal cell carcinomas that develop in patients with basal cell nevus syndrome. The skin examination reveals numerous erythematous papules and plaques, some with overlying scale and crusting, scattered across this patient's back.

Bazex-Dupré-Christol syndrome (follicular atrophoderma with basal cell carcinomas)

Bazex-Dupré-Christol syndrome (BDCS), is a rare X-linked dominant disorder that is defined by pathologic changes in hair follicle structures and the development of multiple BCCs.^{29,30} Acrokeratosis neoplastica, also known, confusingly, as Bazex syndrome, is an unrelated rare paraneoplastic disorder. Oley syndrome is a variant of BDCS in which the clinical presentation is identical but the symptoms spontaneously regress during adulthood.^{31,32} BDCS is characterized by the triad of hypotrichosis, follicular atrophoderma, and BCCs. Milia cysts, hypohidrosis, trichoeplitheliomas, and facial hyperpigmentation are less common findings. Hypotrichosis is diffuse and typically the earliest sign, appreciated shortly after birth. Other signs usually develop by early childhood. BCCs typically develop starting in the second decade, although there are reports involving 3- and 5-year-olds.²⁹ Tumors are usually localized to the face and do not have a typical clinical presentation: they may be pigmented, and can be found in comedones, underneath milium cysts, in zones of follicular atrophoderma, and in lesions that look like pigmented nevi. To date, <20 sporadic and familial cases of BDCS have been reported.²⁹ In 1995, Vabres et al³³ mapped the gene for BDCS to a 23.3-Mb region on chromosome Xq24-27.1,³³ which was confirmed and further refined to an 11.4-Mb interval on Xq25-27.1 in 2011.³⁴ Screening for BCCs should be initiated during the first decade of life and occur 1 to 2 times a year in affected families.²⁹

Rombo syndrome

Rombo syndrome is an autosomal dominant disorder that is characterized by acral erythema, facial

Table II. Summary of the clinical diagnostic criteria for basal cell nevus syndrome

Major criteria	Minor criteria
<ul style="list-style-type: none"> • Multiple (>2) BCCs or 1 BCC by ≤20 years of age • Odontogenic keratocysts of the jaw proven by histology • Palmar or plantar pitting • Bilamellar calcification of the falk cerebri • Bifid, fused, or markedly splayed ribs • First-degree relative with BCNS 	<ul style="list-style-type: none"> • Medulloblastoma • Increased circumference of the head • Congenital malformations: cleft lip or palate, frontal bossing, coarse facies, or moderate or severe hypertelorism • Other skeletal abnormalities: Sprengel deformity, marked pectus deformity, or marked syndactyly of the digits • Radiologic abnormalities: bridging of the sella turcica, vertebral anomalies, such as hemivertebrae, fusion or elongation of the vertebral bodies, modeling defects of the hands and feet, or flame-shaped lucencies of the hands or feet • Ovarian and cardiac fibromas

The diagnosis of BCNS is supported by the finding of either 2 major criteria or 1 major and 2 minor criteria.

Adapted from the criteria outlined by Kiwilsza et al¹² and the 2011 Consensus Statement from the First International Colloquium on Basal Cell Nevus Syndrome.¹⁴

BCC, Basal cell carcinoma; BCNS, basal cell nevus syndrome.

vermiculate atrophoderma, multiple milia, telangiectasias, hypotrichosis, and a propensity to develop BCCs.³⁵ Dermatologic changes first manifest at 7 to 10 years of age, at which time a cyanotic redness and follicular atrophy of sun-exposed skin becomes evident. Only 3 reports of Rombo syndrome, which altogether documented a total of 8 patients, have been published since it was first described by Michaelsson et al³⁵ in 1981. Michaelsson et al's original report described male to male transmission, suggesting an autosomal dominant inheritance pattern.³⁶ The phenotypes of Rombo syndrome and BDCS show a high degree of overlap; distinguishing the 2 clinically can be challenging. There are 3 key differences: (1) in Rombo syndrome, follicular atrophoderma is uncommon and, if seen, is on the elbows and cheeks as opposed to being localized to the dorsal surfaces of the hands; (2) Rombo syndrome is characterized by a reddening of the skin that has not been described in BDCS; and (3) abnormalities in Rombo syndrome only become visible in late childhood.^{29,35-37}

FAMILIAL CANCER SYNDROMES AND NONMELANOMA SKIN CANCER RISK: INCREASED RISK OF SQUAMOUS CELL CARCINOMA

Key points

- There are numerous genodermatoses leading to an increased risk of squamous cell carcinoma; they primarily fall into 1 of the following categories: germline defects in DNA repair leading to increased genomic instability, defects in pigmentation, or

defects in key signaling pathways involved in squamous cell carcinoma development

- Many of the genetic syndromes leading to an increased risk of squamous cell carcinoma are also characterized by an increased risk of other malignancies; therefore, a multidisciplinary management approach with a medical geneticist is recommended for most of these disorders
- Dermatologists play an important role in the diagnosis and management of these conditions because cutaneous findings are often the presenting manifestations of disease

Xeroderma pigmentosum

Xeroderma pigmentosum (XP) is a group of genetic disorders characterized by an inherited hypersensitivity to the DNA-damaging effects of ultraviolet radiation (UVR) due to defects in DNA repair. Patients have a 1000-fold increased risk of cutaneous malignancies, and those not protected from UVR develop NMSC at a median age of 8.5 years. XP is discussed in greater detail in the preceding accompanying article.

Multiple self-healing squamous epithelioma (Ferguson-Smith syndrome)

Cutaneous findings. Multiple self-healing squamous epithelioma (MSSE) is an autosomal dominant disorder that is characterized by the development of crateriform keratoacanthoma-like tumors in sun-exposed areas.³⁸ Tumors begin as reddish macules that subsequently enlarge, ulcerate, often develop a central horny plug, and become locally destructive; after several months, they often regress

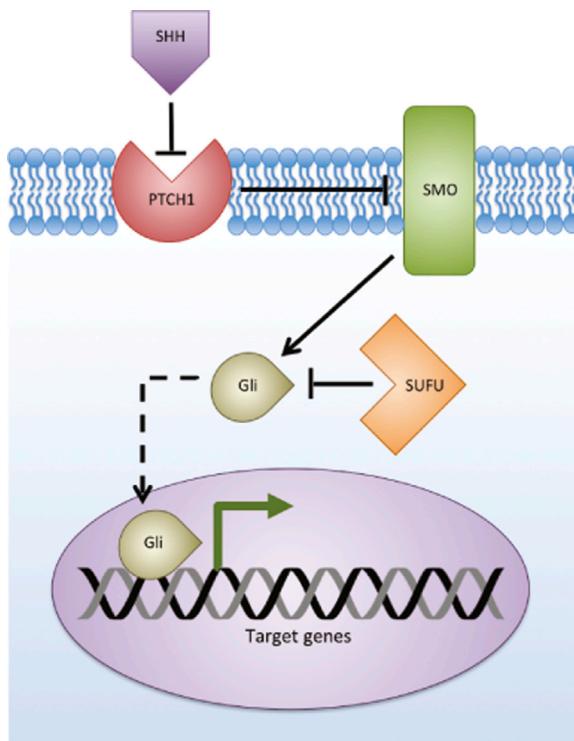


Fig 2. Schematic of the sonic hedgehog (SHH) pathway in a representative keratinocyte. Normally, hedgehog ligand activates the pathway by binding to and inhibiting *PTCH1*, allowing derepression of smoothened (*SMO*), activation of suppressor of fused gene (*SUFU*), and the downstream upregulation of *GLI1* transcription factors that are involved in cell growth and proliferation.

spontaneously, leaving disfiguring pitted scars with irregular edges. The age of onset ranges from 8 to 62 years, with 90% of individuals affected by their 30s to 40s. Patients may have 1 to >100 tumors, with the nose, ears, and circumoral regions being most frequently affected; lesions on the limbs are usually larger and leave flatter scars.^{38,39}

Epidemiology and evaluation. A 1971 review of 62 MSSE cases from 11 independent families in western Scotland suggested that all were derived from a single founder mutation that occurred before 1790.³⁸ Indeed, affected individuals have originated almost exclusively from western Scotland, although MSSE has also been reported in an unrelated Danish family with 11 affected individuals.⁴⁰

Genetics. MSSE is caused by germline inactivating mutations in the transforming growth factor-beta receptor 1 (*TGFBR1*) gene,⁴¹ which encodes a transmembrane kinase receptor involved in TGF- β signal transduction that normally inhibits cell growth.⁴² Of note, germline mutations that activate *TGFBR1* have been described in Loeys–Dietz syndrome, which is characterized by blood vessel abnormalities and skeletal deformities.³⁹

Management. In patients with MSSE, tumors usually involute spontaneously. However, in rare cases, they can progress with unpredictable growth, local destruction, and residual scarring after resolution.⁴³ Therefore, early excision is often performed. Other options include intralesional 5-FU and cryotherapy, but the optimal treatment for tumors in patients with MSSE has not been determined. Although 1 fatal case from local invasive growth has been described, there are no reports to date of metastasis.⁴³

Oculocutaneous albinism

Genetics. Oculocutaneous albinism (OCA) was traditionally a group of 4 autosomal recessive disorders, OCA1, OCA2, OCA3, and OCA4, characterized by absent or decreased melanin synthesis caused by mutations in single genes: *TYR*, *OCA2*, *TYRP1*, and *SLC45A2*, respectively. More recently, 3 additional forms of OCA have been identified: OCA5, OCA6, and OCA7, caused by an unidentified gene mapped to 4q24, *SLC24A5*, and *C10orf11*, respectively.⁴⁴ OCA1 and OCA2 comprise 80% of OCA cases and are the 2 subtypes associated with skin cancer.^{45,46} OCA1 is further subdivided into OCA1A and OCA1B, characterized by complete and partial loss-of-function mutations in *TYR*, respectively. *TYR*'s gene product, tyrosinase, catalyzes the first 2 steps in the melanin biosynthesis pathway. *OCA2* encodes a transmembrane protein that is important for normal melanosome function.

Cutaneous findings. OCA1A is the most severe type of albinism; affected individuals have snow-white hair, white or pink skin that does not tan, and fully translucent blue eyes. OCA1B has a less severe phenotype with variable levels of pigmentation. OCA2 is characterized by decreased melanin, also with variable levels of pigmentation; the phenotype typically includes pink to cream-colored skin, yellow-brown hair, and blue to yellow-brown eyes.^{46,47} The skin begins to show subclinical malignant changes starting in the third decade of life and, without aggressive sun protection, skin cancers develop in the majority of patients; although SCCs are the most common cutaneous malignancies in these patients, BCCs and melanomas also occur at elevated rates compared to the general population.⁴⁸ Cutaneous manifestations are less severe in OCA2.

Epidemiology and evaluation. One in 70 people carry a gene for OCA; however, the prevalence of albinism varies considerably worldwide. OCA2 is most common, with a prevalence of 1 in 36,000 in white individuals and 1 in 3900 to 10,000 in African Americans.⁴⁹ OCA1 has a prevalence of 1 in 40,000 individuals and is uncommon among African Americans.^{46,49} The diagnosis of OCA is clinical

Table III. Summary of the management guidelines for surveillance of both pediatric and adult patients with basal cell nevus syndrome

Pediatric patients	Adult patients
<ul style="list-style-type: none"> • Baseline MRI scan of the brain (repeat yearly until 8 years of age then discontinue; repeat sooner if symptomatic)* • Baseline cardiac ultrasound (repeat if symptomatic) • Baseline skin screen by dermatologist (repeat yearly until first BCC, then every 6 months or more frequently as needed) • Baseline digital panorex of jaw as soon as tolerated (repeat yearly until first jaw cyst, then every 6 months until no jaw cysts for 2 years or until 21 years of age; repeat more regularly if needed) • Baseline spine film at 1 year of age (repeat if symptomatic or per scoliosis protocol every 6 months if abnormal) • Pelvic ultrasound in girls at menarche or age 18, or sooner if symptomatic (repeat if abnormal or symptomatic) • Routine developmental screening (pursue further developmental assessment and cognitive evaluation if failing to meet milestones or difficulty learning in school) • Annual vision, hearing, and speech screening 	<ul style="list-style-type: none"> • Baseline MRI scan of the brain if not performed previously (repeat as needed for symptoms) • Skin screen by dermatologist every 4 months (repeat more frequently if new skin lesions present at each examination) • Digital panorex of jaw annually (repeat as needed for symptoms) • Genetic counseling at baseline and medical genetics evaluation annually • Psychological evaluation as needed • Neurology evaluation annually if previous medulloblastoma (repeat as needed for symptoms) • Obstetrics/gynecology evaluation annually for female patients (repeat as needed for symptoms; pelvic ultrasound at baseline and if symptomatic; maternal fetal medical evaluation for at-risk pregnancies and assessment of fetus for hydrocephalus, macrocephaly, and cardiac fibromas) • Nutritional assessment annually to monitor vitamin A, B, C, and D levels

Adapted from 2011 Consensus Statement from the First International Colloquium on Basal Cell Nevus Syndrome.¹⁴

BCC, Basal cell carcinoma; MRI, magnetic resonance imaging.

*Guidelines may change in coming years in light of recent findings that suppressor of fused gene (SUFU)—related basal cell nevus syndrome patients have a 20-fold higher incidence of medulloblastoma compared to their PTCH1-related counterparts and do not develop jaw keratocysts (Smith et al¹⁹).

and is based on the findings of skin and hair hypopigmentation in conjunction with characteristic ocular symptoms. However, because of the clinical overlap of OCA subtypes, genetic testing can be used to establish the specific defect.^{45,46}

Management. Most people with severe OCA sunburn easily, and sun-protective behavior with regular skin checks is encouraged because of the risk of skin cancer. As in many conditions that necessitate aggressive photoprotection, patients' nutritional status and vitamin D levels should be screened, because supplementation may be required.⁵⁰ Routine ophthalmologic care is also essential in patients with OCA, because ocular problems tend to be the most handicapping sequelae and include impaired visual acuity, severe nystagmus, and strabismus.⁴⁶ Although there is no family history of albinism in most cases, carrier detection and prenatal diagnosis are possible when disease-causing mutations have been identified in families; because lifespan in OCA is not limited, however, these tests are not commonly performed.⁴⁶

Dyskeratosis congenita (Zinsser-Cole-Engman disease)

Dyskeratosis congenita (DC) is a genetically and phenotypically heterogeneous disorder with various

modes of inheritance that is characterized by progressive bone marrow failure, predisposition to malignancy (including acute leukemia and SCC), myelodysplastic syndrome, and pulmonary and hepatic fibrosis.⁵¹ Cutaneous findings usually develop between 5 and 15 years of age and include the triad of nail dystrophy, reticulated pigmentation, and leukoplakia; other findings are premature graying of the hair, alopecia, palmar and plantar hyperkeratosis, and adermatoglyphia. There is an increased risk of mucosal and cutaneous SCCs, particularly of the head and neck, which develop in 30% of leukoplakic areas and appear at a young age.⁵¹ To date, 10 different genes associated with DC have been identified (Table I); they encode products involved in telomere maintenance, and their mutations lead to genomic instability.^{51,52} DC has an annual incidence of <1 in 1 million individuals, and occurs more commonly and has a more severe phenotype in males. Patients with a suspected diagnosis should undergo testing for telomere length and genetic variants, although mutations in 1 of the 10 known genes are found in only 50% to 60% of patients.⁵¹ Regular skin monitoring, especially of leukoplakic plaques, is recommended because of the risk of malignant transformation. A multidisciplinary approach with the inclusion of a medical geneticist

is recommended for managing the multiple other sequelae of DC.⁵¹

Huriez syndrome

Huriez syndrome is a rare autosomal dominant genodermatosis characterized by the triad of diffuse scleroatrophy of the distal extremities, palmoplantar keratoderma, and nail hypoplasia.⁵³ Most case reports involve families from France, although the syndrome has also been reported in Germany, India, and the United Kingdom. The exact genetic basis of the disorder is unknown, but studies have indicated linkage to the 4q23 region.⁵⁴ Patients carry an estimated 15% risk of SCC, which arises in scleroatrophic areas, develops by the third decade of life, and is often particularly aggressive with a poor grade of differentiation and 5% rate of associated mortality from metastasis; this fact underscores the importance of early diagnosis.⁵⁵⁻⁵⁷ Close dermatologic surveillance for malignancies and a high index of suspicion with aggressive treatment of confirmed SCC is recommended because of the pernicious nature of malignancy in this disease.⁵⁶

Epidermolyticus verruciformis (Lewandowsky-Lutz dysplasia)

Epidermolyticus verruciformis (EV) is an autosomal recessive disease affecting <1 in 1,000,000 individuals that is characterized by generalized non-resolving verrucous lesions caused by abnormal susceptibility to cutaneous human papilloma (HPV) infections.⁵⁸ It is caused by mutations in the epidermolyticus verruciformis 1 (*EVER1*) or *EVER2* genes, which encode proteins that regulate zinc homeostasis and interact with certain HPV proteins.⁵⁹ The first clinical manifestations, which present as verrucae planae-like lesions on the extremities and pityriasis versicolor-like macules on the trunk, typically develop during infancy or childhood. Approximately 50% of patients with EV develop SCCs in sun-exposed areas, most of which are localized^{58,60}; however, lesions harboring only HPV-22b can transform into aggressive malignant SCC. Regular skin examinations are recommended in affected individuals.⁶⁰

Rothmund-Thomson, Bloom, and Werner syndromes

Rothmund-Thomson syndrome (RTS), Bloom syndrome, and Werner syndrome are rare autosomal recessive disorders with overlapping phenotypes caused by mutations in the *RECQL4*, *RECQL3*, and *RECQL2* genes, respectively (Table IV).⁶¹⁻⁷¹ These genes encode helicases involved in DNA synthesis and repair and mutations lead to telomere

dysfunction and sustained genomic instability. All 3 syndromes are characterized by an increased risk of SCC.

Other syndromes

Other genetic syndromes associated with an increased risk of SCC not discussed here include *GATA2* deficiency, *DOCK8* deficiency, Fanconi anemia, and epidermolysis bullosa.⁷²⁻⁷⁸

FAMILIAL CANCER SYNDROMES AND NONMELANOMA SKIN CANCER RISK: INCREASED RISK OF OTHER NONMELANOMA SKIN CANCERS

Key points

- Adenosine deaminase severe combined immunodeficiency is a rare immunodeficiency syndrome that is associated with a high incidence of dermatofibrosarcoma protuberans; unlike dermatofibrosarcoma protuberans in the general population, dermatofibrosarcoma protuberans in patients with adenosine deaminase severe combined immunodeficiency typically demonstrates multicentricity and occurrence at an early age
- Muir-Torre syndrome is an autosomal dominant condition caused by germline mutations in mismatch repair genes that is characterized by the development of sebaceous gland tumors, keratoacanthomas, and visceral malignancies

Adenosine deaminase severe combined immunodeficiency

Adenosine deaminase severe combined immunodeficiency (ADA-SCID) is a rare disorder that is characterized by the dysfunction of T, B, and natural killer (NK) cells. It has an incidence of 1 in 200,000 individuals and comprises 15% of all SCID cases.⁷⁹ Mutations in *ADA1*, which encodes a ubiquitous enzyme involved in purine metabolism, lead to a toxic intracellular accumulation of adenosine and deoxyadenosine, causing the disease phenotype.⁸⁰ Clinically, 90% of patients manifest the classic SCID phenotype of life-threatening infections, chronic persistent diarrhea, hepatosplenomegaly with the absence of palpable lymph nodes, and failure to thrive in the first months of life. Without treatment, the disease is fatal in 1 to 2 years in these patients; however, milder phenotypes have also been described.^{81,82} Dermatologically, ADA-SCID was recently reported to be associated with a high incidence of dermatofibrosarcoma protuberans (DFSP); the mechanism for the clustering of these 2

Table IV. Comparison of the phenotype, genetics, epidemiology, evaluation, and management of Rothmund–Thomson, Bloom, and Werner syndromes

Phenotype	Genetics	Epidemiology and evaluation	Management
RTS	<ul style="list-style-type: none"> Characterized by poikiloderma, sparse hair, palmoplantar hyperkeratotic lesions, and early aging of the skin Hallmark rash usually develops between 3–6 months of age (although late-onset poikiloderma has been reported) and is marked by facial erythema, swelling, and blistering, which subsequently spreads to the extremities and buttocks, eventually resulting in poikiloderma 	<ul style="list-style-type: none"> Caused by mutations in <i>RECQL4</i> Analysis by of 33 patients by Wang et al suggested 2 subtypes of RTS: type I, which is characterized by the characteristic cutaneous findings and negative for the <i>RECQL4</i> mutation, and type II, which has a predisposition to osteosarcoma in addition to cutaneous findings and is caused by truncating and other deleterious mutations in <i>RECQL4</i> 	<ul style="list-style-type: none"> Approximately 300 patients have been reported in the literature to date (patients with atypical clinical presentation may be overlooked because of the highly variable clinical spectrum) Described in all ethnic groups; there does not appear to be a founder effect in any specific population Diagnosis is made based on the characteristic childhood rash, but should be considered in all patients with osteosarcoma, especially if there are associated skin changes <i>RECQL4</i> genetic testing is recommended for patients with RTS syndrome in whom the diagnosis is unclear because of overlapping clinical signs with other genodermatoses, and in patients with a clinical presentation at the interface of 2 distinct <i>RECQL4</i> syndromes
BS	<ul style="list-style-type: none"> Characterized by immunodeficiency with recurrent infections, proportionate small stature with microcephaly, chronic pulmonary disease, diabetes, infertility, and predisposition to cancer Cutaneous features include poikiloderma and a characteristic photosensitive facial erythema with telangiectasia in a butterfly distribution that presents early in life 	<ul style="list-style-type: none"> Caused by mutations in the <i>BLM</i> or <i>RECQL3</i> gene at 15q26.1 	<ul style="list-style-type: none"> Approximately one-third of BS patients are Ashkenazi Jews, who have a carrier frequency of 1%. Approximately 170 cases have been reported in the US Cutaneous SCC or BCC develops in 15% of all patients with BS, with a mean age of onset of 31.7 years The dermatologic sequelae of BS show considerable overlap with other conditions such as RTS, erythropoietic protoporphria, and Cockayne syndrome, and a timely diagnosis is crucial for the initiation of cancer screening Suspected diagnosis should be confirmed with DNA sequencing. Genetic and prenatal testing is recommended for high-risk carrier populations, such as Ashkenazi Jews

- WS
 - Characterized by premature aging and graying of hair, short stature, hoarseness, cataracts, diabetes, premature atherosclerosis, muscular atrophy, and a predisposition to cancer, including soft tissue sarcomas and meningiomas
 - Cutaneous findings include regional atrophy of subcutaneous fat, pigmented and sclerodermatosus changes, and deep, chronic ulcers around the Achilles tendon
 - Caused by biallelic mutations in the *WRN* or *RECQL2* gene on 8p12-p11.2
 - Approximately 100 different mutations have been identified
-
- The frequency of Werner syndrome in Japan is estimated to be about 3 per million people
 - Skin cancers comprise 20% of the malignancies reported in patients with WS, and the vast majority are SCCs

BCC, Basal cell carcinoma; BS, Bloom syndrome; NMSC, nonmelanoma skin cancer; RTS, Rothmund–Thomson syndrome; WS, Werner syndrome.

extremely rare conditions remains unknown, but, given the immunodeficient state in ADA-SCID, an infectious cause has been hypothesized.⁸³ In the general population, the incidence of DFSP is 4.2 per 1,000,000,⁸⁴ with <200 reported cases in the pediatric population; it typically presents as a solitary subcutaneous nodule. In patients with ADA-SCID, however, DFSP often demonstrates multicentricity (4–15 lesions), occurrence at an early age (mean, 8.9 years), and may have an incidence as high as 67%.⁸³ Lesions typically present in the preprotuberant morpheaform plaque stage, which may be overlooked and difficult to distinguish from scars or areas of benign pigmentation when small; therefore, dermatologists should have a high clinical suspicion and screen regularly for DFSP in patients with ADA-SCID.⁸³

Muir–Torre syndrome

Muir–Torre syndrome (MTS) is an autosomal dominant condition that is characterized by the development of sebaceous gland tumors and visceral malignancies, typically colorectal or genitourinary tumors.

Cutaneous findings. Sebaceous tumors present at a median age of 53 years as firm, yellowish, or skin-colored papules or nodules, typically <0.5 cm in diameter and arising on the face or scalp.^{85,86} About 25% of individuals also develop keratoacanthomas, and a smaller number develop BCCs of the head and neck.⁸⁶

Genetics. MTS is caused by germline mutations in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, and *PMS2*, the same genes that are affected in hereditary nonpolyposis colon cancer (HNPCC); however, the hallmark sebaceous tumors of MTS are absent in patients with HNPCC.^{87–89} In addition, the majority of MTS cases are caused by mutations in *MSH2*, whereas mutations are equally distributed across MMR genes in HNPCC.⁸⁷ These genes encode enzymes responsible for repairing errors generated during DNA replication and deficiency leads to microsatellite instability.⁹⁰

Epidemiology and evaluation. Approximately 200 cases of MTS have been reported, with a male:female ratio of 3:2 and a median age at diagnosis of 55 years.⁸⁶ Because sebaceous tumors are exceedingly rare in the general population and are so strongly associated with MTS, most experts recommend screening all sebaceous neoplasms for MMR defects and subsequently performing genetic testing if the results are abnormal (Fig 3).⁸⁶

Management. Dermatologists are crucial in the diagnosis and management of MTS; because sebaceous tumors often precede the development of

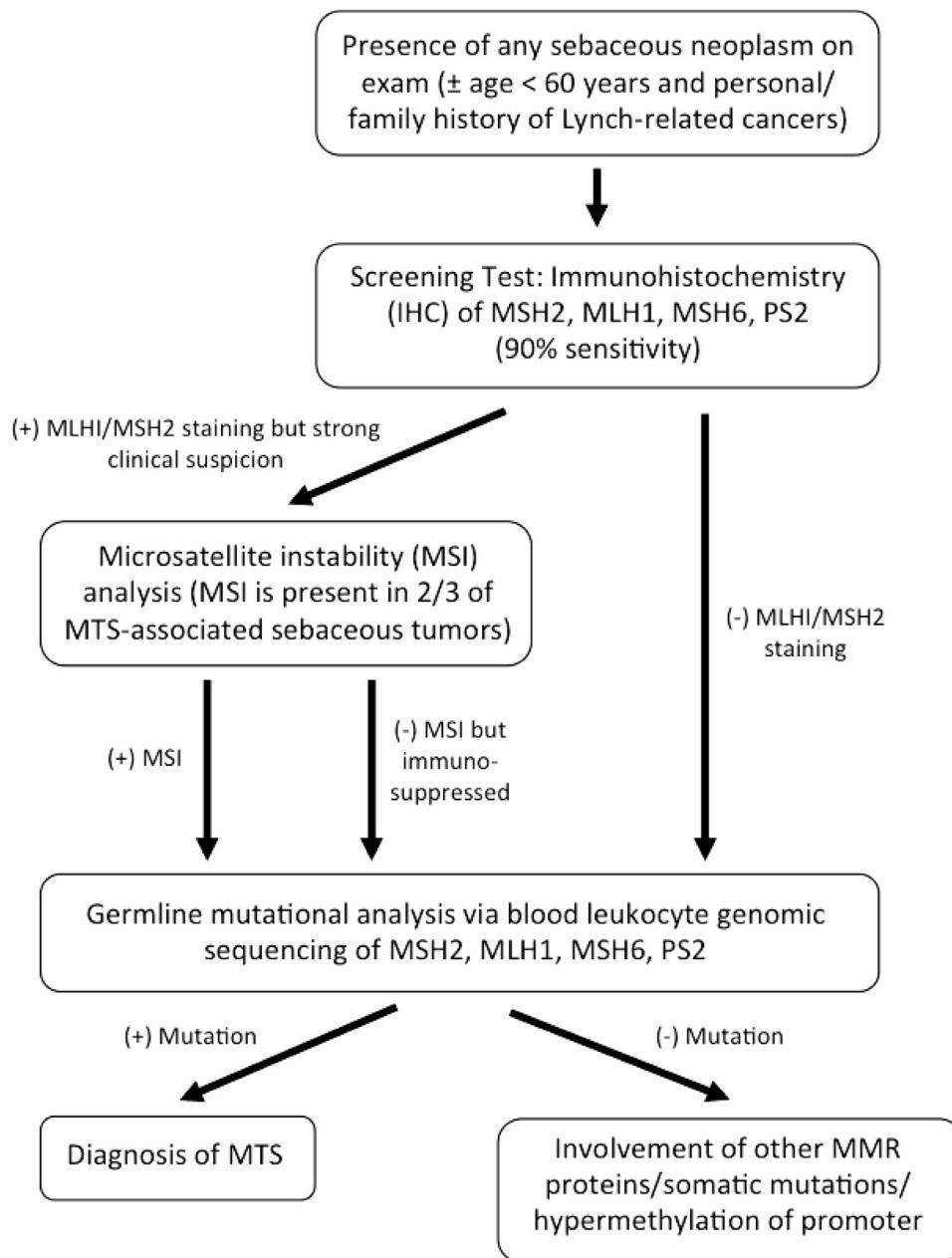


Fig 3. Flowchart of diagnostic workflow for patients with suspected Muir–Torre syndrome. All sebaceous neoplasms should undergo immunohistochemistry as a screening test, followed by microsatellite instability analysis or germline mutational analysis depending on the results.

internal malignancies, early diagnosis of MTS is critical. Affected individuals and first-degree relatives should undergo regular cancer screening, including annual skin examinations.^{86,91}

CONCLUSION

In conclusion, NMSCs are uncommon in pediatric patients, and the diagnosis of skin cancer at a young age often points to an underlying genetic condition. Recent advances in genomics promise to change the way in which these conditions are diagnosed and

managed, and dermatologists play a critical role in this process. In general, genetic testing is used in 2 situations: (1) to confirm the clinical diagnosis of a genetic disease or (2) to predict the probability of a genetic condition in an individual or family (eg, prenatal diagnosis, newborn screening, carrier screening, and determining risks to relatives of affected individuals). Although genetic testing is a formidable tool, the paucity of scientific information on many genetic conditions and its myriad practical and psychosocial considerations—including issues

of discrimination, confidentiality, anxiety, DNA banking, and interpretation of results—make genetic testing a complex decision that should be made together by the clinician and patient. The American Society of Clinical Oncology recommends offering genetic testing when an individual has personal or family history features suggesting a hereditary cancer susceptibility condition, the test results can be accurately interpreted, and the results will influence the diagnosis and/or management of patients or family members.⁹² Table I summarizes tests that are currently commercially available for the conditions described in this paper. As next-generation sequencing technologies become increasingly cost-effective, genetic testing will likely play a larger role in clinical practice.

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Wound healing and treating wounds

Differential diagnosis and evaluation of chronic wounds

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Learning objectives

After completing this learning activity, participants should be able to describe the physiologic steps of wound healing; generate a thorough differential for acute and chronic wounds; and commence the appropriate work-up for accurate and expedient diagnosis.

Disclosures

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Wounds are an excellent example of how the field of dermatology represents a cross-section of many medical disciplines. For instance, wounds may be caused by trauma, vascular insufficiency, and underlying medical conditions, such as diabetes, hypertension, and rheumatologic and inflammatory disease. This continuing medical education article provides an overview of wound healing and the pathophysiology of chronic wounds and reviews the broad differential diagnosis of chronic wounds. It also describes the initial steps necessary in evaluating a chronic wound and determining its underlying etiology. (J Am Acad Dermatol 2016;74:589-605.)

Key words: chronic wounds; chronic wound differential diagnosis; chronic wound evaluation; chronic wound work-up; wound healing; wound pathophysiology.

INTRODUCTION

Wound management often falls within dermatologists' scope of practice. We create acute surgical wounds and frequently see poorly healing ulcers in our clinics. In this article, we briefly discuss the physiology of wound healing, the causes of poor wound healing, the broad differential diagnoses for chronic wounds, and the appropriate steps for clinical evaluation of chronic wounds.

WOUND HEALING

Acute wounds undergo a well understood series of steps as they heal. In chronic wounds, these steps

Abbreviations used:

ABI:	ankle brachial index
CVI:	chronic venous insufficiency
DFU:	diabetic foot ulcer
MMP:	matrix metalloproteinase
MPA:	microscopic polyangiitis
PAN:	polyarteritis nodosa
PDGF:	platelet-derived growth factor
PG:	pyoderma gangrenosum
PU:	pressure ulcer
SCC:	squamous cell carcinoma
TGF- β :	transforming growth factor-beta
VLU:	venous leg ulcer

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are disrupted. Researchers continue to work to understand the pathophysiology of nonhealing wounds, and several of the most important factors will be discussed below.

NORMAL WOUND HEALING

Key points

- **The 4 phases of normal wound healing include hemostasis, inflammation, proliferation/repair, and remodeling**
- **Macrophages are the most important inflammatory cell in wound healing—they phagocytose pathogenic organisms, degrade debris, and stimulate granulation tissue formation**
- **Fibroblasts are essential for proliferation and lay down important structural elements, including collagen, elastin, and extracellular matrix proteins**
- **During the remodeling process, which can take weeks to years, type III collagen is converted to type I collagen**
- **Mature scar strength is about 80% of that of unwounded skin**

Wound healing occurs in 4 overlapping phases: hemostasis, inflammation, proliferation, and remodeling.

Hemostasis occurs via a fibrin and platelet plug, which triggers the coagulation cascade. Damage to endothelial cells exposes collagen that stimulates platelets to undergo activation, adhesion, and aggregation. Platelets produce chemotactic factors, including platelet-derived growth factor (PDGF) and transforming growth factor- β (TGF- β). These growth factors attract macrophages, neutrophils, fibroblasts, endothelial cells, and smooth muscle cells,¹ which are essential for the inflammatory and proliferative phases. Fibrin, derived from platelet-derived fibrinogen, acts as a matrix for incoming macrophages and fibroblasts.²

The inflammatory phase begins as neutrophils adhere to endothelium within minutes of trauma.³ Neutrophils use elastase and collagenase to facilitate migration into the extracellular space, where they phagocytose bacteria, degrade matrix proteins, and attract additional neutrophils and macrophages.³ Macrophages are arguably the most important inflammatory cell in the acute healing process, dominating within 3 to 5 days.⁴ They phagocytose pathogenic organisms, degrade wound debris, and stimulate granulation tissue formation and angiogenesis. Macrophage growth factors include PDGF, TGF- β , fibroblast growth factor, interleukin-1, interleukin-6, and tumor necrosis factor- α .⁵ TGF- β

is particularly important, stimulating macrophages and influencing fibroblast function, chemotaxis, and collagen deposition.⁴

The proliferation phase encompasses fibroplasia, granulation, epithelialization, and angiogenesis and begins within 24 hours of wound infliction. An early fibrin matrix allows keratinocytes, in part stimulated by TGF- β , to migrate from the wound edge and hair follicles and slide over keratinocytes already in the wound bed in a “leap-frogging” action.^{1,5,6} Concurrently, vascular endothelial growth factor, upregulated by low oxygen tension, promotes angiogenesis.^{5,7} Nearby capillary endothelial cells are recruited¹ and stimulated to proliferate by vascular endothelial growth factor, which also induces smooth muscle cell migration.⁸

Fibroblasts, which migrate in between 48 and 72 hours postinjury, are important for dermal matrix proliferation, regulated by PDGF, fibroblast growth factor, and others.⁹ Fibroblasts produce structural proteins, including collagen, elastin, extracellular matrix proteins, and matrix metalloproteinases (MMPs). MMPs degrade the initial fibrin plug and facilitate fibroblast movement.⁹ Collagen is apparent 48 to 72 hours after the wound appears and is maximally secreted between postinjury days 5 to 7. Type III collagen (fetal collagen) is initially more dominant, stimulated by TGF- β .¹ Glycosaminoglycans and proteoglycans, components of the extracellular matrix, provide strength, support, and density.¹

The remodeling process takes weeks to years. Wound contraction begins by day 5 because of the phenotypic change of fibroblasts into actin-laden myofibroblasts.¹⁰ MMPs and tissue inhibitors of metalloproteinases reorganize type III collagen fibers into a stronger network of type I collagen.¹

Collagen reaches ~20% of its tensile strength after 3 weeks and 80% strength at 12 months. The maximum scar strength is 80% of that of unwounded skin.

CHRONIC VERSUS ACUTE WOUNDS

Key points

- **Wound healing time depends on multiple factors, including wound size, depth, location, patient age, and local and systemic disease**
- **Acute wounds progress through the phases of healing in a normal and timely manner**
- **Chronic wounds fail to progress through a normal orderly and timely sequence of repair or without restoring normal anatomy and function**

Table I. Characteristics of acute versus chronic wounds

Acute wounds	Chronic wounds
Low levels of bacteria	High levels of bacteria (MRSA)
Low inflammatory cytokines	High inflammatory cytokine levels
Low protease and reactive oxygen species levels	High protease and reactive oxygen species levels
Intact functional matrix	Degraded nonfunctional matrix
High mitogenic activity	Low mitogenic activity
Mitotically competent cells	Senescent cells

MRSA, Methicillin-resistant *Staphylococcus aureus*.

Adapted from Mast and Schultz.¹¹

- **Normal healing is regulated by cytokines, growth factors, and proteases**
- **Poor wound healing is characterized by chronic inflammation, cellular senescence, poor cytokine milieu, and critical bacterial colonization**
- **Chronic wounds have elevated levels of cytokines and proteases that destroy essential extracellular matrix components, growth factors, and growth factor receptors**

Macroscopically, wound healing depends on multiple factors, including wound size, depth, and location, patient age, and the presence of local or systemic disease. At the molecular level, healing wounds show low levels of bacteria, inflammatory cytokines, proteases, and reactive oxygen species. They exhibit intact functional matrix, high mitogenic activity, and mitotically competent cells. Multiple factors contribute to poor wound healing, including reduced oxygenation, chronic inflammation, fibroblast senescence, impaired function, and levels of critical cytokines, growth factors and their receptors, abnormal MMP activity, and bacterial colonization and infection¹¹ (Table I).

In culture, fibroblasts from acute wounds are mitotically competent with high mitogenic activity, but chronic wound fibroblasts are senescent with low mitogenic capacity.^{5,12,13}

Wound fluid from acute wounds, such as split-thickness skin graft donor sites, stimulates fibroblast proliferation in culture, indicating a growth-promoting molecular milieu.¹² In contrast, chronic wound fluid inhibits fibroblast and keratinocyte proliferation.¹³⁻¹⁵ Cytokine and growth factor receptors, such as type II TGF- β receptor, may also be downregulated or improperly functioning in chronic wounds.^{16,17}

Table II. Systemic and local factors contributing to chronic wounds

Systemic
Age
Malnutrition
Medications (eg, corticosteroids and immunosuppressants)
Obesity
Chronic medical conditions (eg, cardiac failure, connective tissue disease, hypoxia, endocrine disorders, vascular disease, diabetes, cancer, and immunosuppression)
Habits (eg, smoking and alcohol consumption)
Local
Vascular disease (venous and arterial)
Neuropathy or pressure
Infection
Necrotic tissue in the wound bed or excessive wound tension
Unfavorable local environment (ie, inappropriate topical products or dressings, contact dermatitis, or wound that is too dry or too wet)
Inappropriate treatment (eg, debridement for pyoderma gangrenosum)
Malignant wound
Repetitive trauma
Radiation

MMPs are overactive in chronic wounds, with decreased levels of tissue inhibitors of metalloproteinases.¹⁸⁻²² These high levels of proteases in chronic wounds degrade the tissue matrix and impair healing.

Recent research does not support a clear correlation between microbial load and wound healing,²³ but we know that there is a continuum of wound infection, ranging from contamination, where bacteria do not multiply or cause clinical infection, to systemic infection. Biofilms are a significant problem in chronic wounds. They are composed of a community of bacteria that secretes a matrix or glycocalyx, which is protective against the host immune response and difficult to eradicate. Bacteria (both planktonic and biofilms) cause inflammation, which leads to the release of proteases and reactive oxygen species from inflammatory cells. Bacteria also secrete exotoxins and proteases that degrade proteins that are essential for healing. Biofilms have been identified in 60% of biopsy specimens obtained from chronic wounds but only 6% of biopsy specimens obtained from acute wounds.²⁴

DIFFERENTIAL DIAGNOSIS OF CHRONIC WOUNDS

Chronic wounds can result from multiple systemic and local factors (Table II), and the differential

Table III. Extended differential diagnosis for chronic wounds

Infection-related

Bacterial

Erysipelas bullosa, necrotizing fasciitis (*Streptococcus haemolyticus*), botryomycosis (commonly *Staphylococcus aureus*), gas gangrene (*Clostridium* species), ecthyma gangrenosum (*Pseudomonas aeruginosa*), septic embolism, bacterial endocarditis, anthrax (*Bacillus anthracis*), diphtheria (*Corynebacterium diphtheriae*), meningococcemia (*Neisseria meningitidis*), bartonellosis (*Bartonella bacilliformis*), glanders (*Burkholderia mallei*), malakoplakia (commonly *E. coli*), tularemia (*Francisella tularensis*), and yaws (*Treponema pallidum pertenue*)
Sexually transmitted anogenital ulceration: syphilis (*Treponema pallidum*), granuloma inguinale (*Klebsiella granulomatis*), lymphogranuloma venereum (*Chlamydia trachomatis*), and chancroid (*Haemophilus ducreyi*)

Atypical mycobacterial

Leprosy (*Mycobacterium leprae*), buruli ulcer (*M ulcerans*), tuberculosis (*M tuberculosis* causing ulcerating cutaneous tuberculosis, lupus vulgaris, and papulonecrotic tuberculid)
Viral: herpes simplex, varicella zoster, cytomegalovirus
Fungal: bullous tinea pedis, eumycotic mycetoma, chromoblastomycosis, coccidiomycosis, sporotrichosis, histoplasmosis, and blastomycosis
Protozoan: Leishmaniasis, amoebiasis (*Entamoeba histolytica*), and acanthamoeba

Medication-induced

Hydroxyurea
Methotrexate
Chemotherapeutics
Immunosuppressives
Bacillus Calmette-Guerin vaccination

Malignancy-related

Internal malignancy metastasis
Cutaneous malignancy
Squamous cell carcinoma (Marjolin ulcer)
Basal cell carcinoma
Melanoma (including acral and amelanotic types)
Merkel cell carcinoma
Kaposi sarcoma
Malignant fibrous histiocytoma
Lymphoproliferative malignancy

Medical conditions

Diabetes mellitus
Neuropathic conditions including tabes dorsalis, paraplegia, and multiple sclerosis
Klinefelter syndrome
Hypertension (Martorell ulcer)

Blood disorders

Polycythemia vera
Sickle cell anemia
Thrombocytopenia (including thrombotic thrombocytopenic purpura)
Paraproteinemia

Autoimmune conditions

Scleroderma
Rheumatoid arthritis
Cutaneous lupus erythematosus
Inflammatory bowel disease (including metastatic Crohn's disease)
Nutrition (caloric, protein, vitamin, and mineral deficiencies)

Pressure

Primary skin conditions

Necrobiosis lipoidica
Sarcoidosis
Ulcerative pyoderma gangrenosum
Panniculitis (including erythema induratum)
Bullous diseases (including bullous pemphigoid, pemphigus, bullous lichen planus, and porphyria cutanea tarda)
Stevens-Johnson syndrome and toxic epidermal necrolysis

Continued

Table III. Cont'd

Substance abuse-related (Fig 1)
Skin-popping
Toxic and irritant properties of illicit drugs and adulterants
Vasoconstrictive cocaine
Bacterial embolism
Trauma (including burns, bites, and postsurgical injury)
Factitious (including dermatitis artefacta, malingering, and Munchausen by proxy)
Vascular
Venous leg ulcers
Chronic venous insufficiency
Congenital valvular insufficiency
Trauma-related valvular insufficiency
Thrombus-related valvular insufficiency (deep venous thrombosis)
Mixed venous-arterial or venous-lymphatic insufficiency
Arteriovenous malformation
Arterial leg ulcers
Atherosclerosis-related
Embolism-related
Thromboangiitis obliterans
Vasculitis
Small-vessel vasculitis: leukocytoclastic vasculitis, microscopic polyangiitis, granulomatosis with polyangiitis (formerly Wegener granulomatosis), Churg-Strauss, Henoch-Schönlein purpura, cryoagglutination (cryoglobulins, cryofibrinogen), and Behçet disease
Medium-sized vessel: polyarteritis nodosa
Vasculopathy
Hypercoagulopathic disorders (Table VI)
Disseminated intravascular coagulation and purpura fulminans
Sneddon syndrome (usually presenting as livedo reticularis)
Cholesterol emboli
Calciphylaxis
Warfarin-induced necrosis (and heparin necrosis)
Livedoid vasculopathy
Dego disease (malignant atrophic papulosis)

diagnosis for chronic, nonhealing ulcers is extensive (Table III). Venous leg ulcers (VLUs), arterial ulcers, and diabetic foot ulcers (DFUs) are the most common wounds seen on the lower extremities (Table IV).

COMMON LOWER EXTREMITY ULCERS AND PRESSURE ULCERS

Key points

- **The most common types of lower extremity ulcers are venous leg ulcers, arterial ulcers, and diabetic foot ulcers**
- **Venous leg ulcers occur in the gaiter area (between the lower calf and ankle), and are associated with edema, hemosiderin pigment, venous eczema, and lipodermatosclerosis**
- **Arterial ulcers are more common in smokers and patients with diabetes mellitus, hyperlipidemia and hypertension; they are**



Fig 1. Chronic ulcer caused by illicit drug use. Ulcer on the shin of a man who used his wound as an access site for the injection of illicit drugs for many years. (Courtesy of Jennifer Gloeckner-Powers, MD.)

Table IV. Comparison of venous leg ulcers, arterial ulcers, and diabetic foot ulcers

Ulcer type	Location	Clinical appearance	Associated symptoms
Venous leg ulcer	Gaiter region of the lower leg (midcalf to 1 in inferior to the malleolus)	Single or multiple lesions; irregularly shaped and shallow; commonly with granulation and fibrinous tissue and rarely with necrotic tissue; lower extremity edema; venous eczema, hemosiderin deposition, or lipodermatosclerosis; inverted champagne bottle appearance of the lower leg	Pain may or may not be present; aching in the legs after long periods of standing; leg heaviness and swelling
Arterial ulcer	Distal extremities and sites of trauma, such as bony prominences	Sharply demarcated borders; dry, necrotic wound bed; sparse granulation tissue; signs of arterial insufficiency, such as cool extremities and poor peripheral pulses, hair loss, atrophic skin, and delayed capillary refill time	Ulcer pain, often severe; claudication (leg pain with exercise or at rest); pain that worsens with leg elevation and improves with dependency
Diabetic foot ulcer	Plantar surfaces and sites of repetitive trauma and increased pressure	Often with punched out borders; may be associated with callus, foot deformity, or limited joint mobility; pink, warm, dry skin; signs of fissuring and skin breakdown	Distal anesthesia or paraesthesia consistent with diabetic neuropathy; claudication

painful, distal, and often dry or necrotic with poor granulation tissue

- **Diabetic foot ulcers are usually caused by peripheral neuropathy or angiopathic changes; they are most common at sites of repetitive pressure, such as the soles of the feet**
- **Pressure ulcers affect up to 5% of hospitalized patients and often occur over bony prominences**

Venous leg ulcers

VLU, caused by chronic venous insufficiency (CVI), comprise 50% to 70% of leg ulcers,²⁵ with a prevalence of 1% to 1.5%.²⁶ Patients may report swelling and lower extremity aching worsening during the day and improving with elevation. The history may include deep venous thrombosis, trauma, or surgery to the lower leg.²⁷

VLUs are often located in the gaiter region (Fig 2), an area extending from midcalf to approximately 1 in below the malleolus. They may be single or multiple and are irregularly shaped but shallow. Red granulation tissue or yellow fibrinous tissue is common; black necrotic tissue is rare. Skin changes include varicosities, pitting edema, dermatitis, hemosiderin pigment, and lipodermatosclerosis²⁸ (Fig 3).

The diagnosis of a VLU can often be made clinically, but about 25% of patients with venous reflux will not show typical clinical changes. Duplex

ultrasonography is helpful in assessing reflux and obstruction.^{28,29} For superficial, deep femoral, and deep calf veins, the cutoff value for length of reflux is >500 ms. In the perforating veins, it is >350 ms; in the common femoral, femoral, and popliteal veins it is >1000 ms.³⁰ Venography is rarely recommended in postthrombotic disease.³¹ The ankle–brachial index (ABI) should be performed to rule out concurrent arterial disease.^{32,33}

It has been shown that log healing rate, log wound area ratio, and percentage change in wound area can be used as surrogate markers to predict VLU healing at the 12- or 24-week mark.³⁴ For example, a wound <10 cm² in area and <12 months old has a 29% chance of not healing by week 24 of compression therapy. A wound >10 cm² in area and >12 months old has a 78% chance of not healing.³⁵

Arterial leg ulcers

Arterial disease accounts for up to 25% of leg ulcers.³⁶ Atherosclerosis causes poor perfusion, inadequate skin oxygenation, and tissue breakdown.³⁶ Diabetes, smoking, hyperlipidemia, hypertension, obesity, and increased age are important risk factors.³⁷ Patients may report claudication and pain worsening with leg elevation and improving with dependency.

Arterial ulcers frequently present over sites of pressure or trauma, such as bony prominences, or at



Fig 2. Gaiter region. The gaiter region (located between the 2 blue arrows) includes the lower leg from midcalf to approximately 1 in inferior to the malleolus.



Fig 3. Venous leg ulcer. This ulcer is characterized by an irregular shape, shallow depth, and a fibrinous base. (Courtesy of Tania J. Phillips, MD.)

distal points, such as the toes. They appear punched out with sharply demarcated borders and have dry, necrotic wound beds. Granulation tissue is sparse. Clinical findings include hair loss, atrophic skin, poor peripheral pulses, and capillary refill time >3 to 4 seconds.³⁸ Femoral bruits indicate proximal atherosclerotic lesions, and delayed filling of veins on dependency may result in bright pink or red extremities.³⁸ Confirmation tests include ABIs, Doppler arterial waveform analysis, and transcutaneous oxygen pressure measurements.³⁶ Peripheral arterial disease (PAD) is diagnosed when the ABI is ≤ 0.9 . PAD is mild to moderate when the ABI is 0.4 to

0.9 and severe when ABI is <0.4 . An ABI >1.3 is also abnormal and may represent noncompressible vessels.³⁹ Normal transcutaneous oxygen pressure values depend on age and position (ie, higher for younger patients and more proximal measurements). Normal levels are approximately 60 mm Hg, and levels ≤ 20 mm Hg suggest that revascularization will improve wound healing.⁴⁰ Arteriograms and computed tomography or magnetic resonance imaging scans may be useful to map any vascular occlusion.

Diabetic foot ulcers

DFUs affect 4% to 10% of patients with diabetes annually,^{41,42} and are the leading cause of hospitalization and amputation in these patients.^{41,42} Neuropathy and ischemia are the most common causes, with infectious sequelae occurring frequently.^{41,43,44} Between 50% and 60% of patients with a DFU have signs of infection at the time of hospital admission.^{45,46}

In diabetes, autonomic deficits lead to deficient sweating and altered blood flow regulation, resulting in impaired distal extremity oxygenation and warm, dry skin susceptible to fissuring and break down.^{44,47,48} Up to 50% of ulcers are ischemic or neuroischemic in origin,⁴⁷ with poor glucose control accelerating arterial disease.⁴⁹

DFUs are commonly located on plantar surfaces at sites of repetitive trauma. Calluses form at abnormal pressure points because of neuropathy, deformities (eg, Charcot foot), or limited joint mobility.⁵⁰ Distal extremities may be dry, pink, and warm. Sensation with the nylon monofilament, Achilles tendon reflex, and 128-Hz tuning fork testing may be abnormal.^{41,44} ABIs are indicated to evaluate for PAD, but can often be falsely elevated because of vessel calcification. Vascular imaging may be helpful, including duplex ultrasonography, computed tomography angiography, or magnetic resonance angiography.

Pressure ulcers

Pressure ulcers (PUs) are localized areas of tissue necrosis that result from unrelieved pressure, leading to localized tissue injury. They are commonly found over bony prominences. PUs affect 1% to 5% of hospitalized patients^{51,52} and up to 26.2% of patients presenting to the emergency department from nursing homes.⁵³ The main etiologic factors include pressure, shearing forces, friction, and moisture^{54,55} (Fig 4).

Risk factors include decreased level of consciousness, malnutrition, impaired mobility, and fecal incontinence.⁵⁶ PUs are categorized from stage I to IV, based on depth⁵⁵ (Table V).

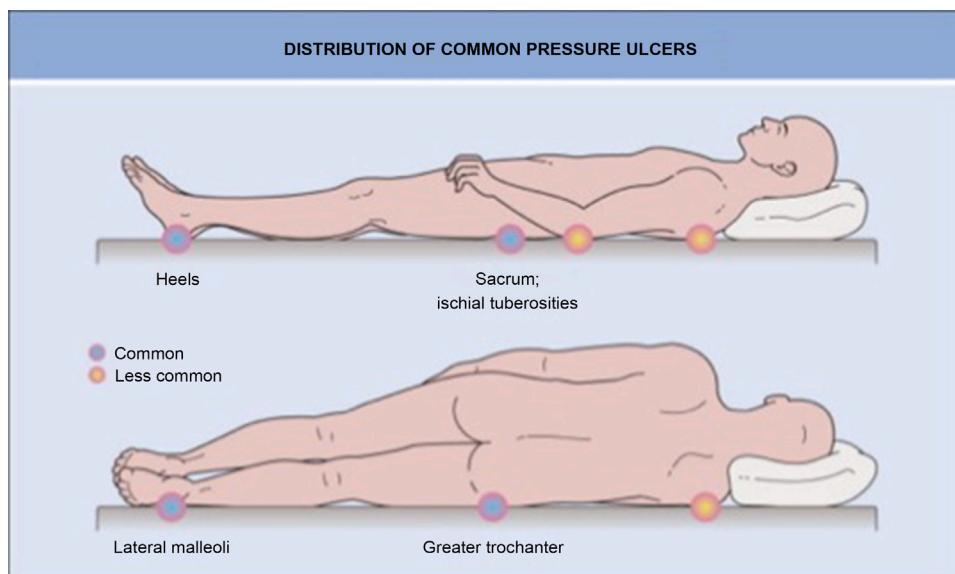


Fig 4. The distribution of common pressure ulcers. (Reproduced with permission from Phillips TJ. Ulcers. Dermatology, vol 2. Philadelphia: Elsevier; 2008: p 1611.)

Table V. Pressure ulcer classification⁵⁵

Stage I	Nonblanchable erythema
Stage II	Partial-thickness, shallow open ulcer with red pink wound bed without slough; may present as a blister
Stage III	Full-thickness skin loss. Subcutaneous fat may be visible, but bone, tendon or muscle are not exposed; slough may be present but does not obscure depth of tissue loss; may include undermining and tunneling
Stage IV	Full-thickness tissue loss with exposed bone tendon or muscle; slough or eschar may be present; often includes undermining and tunneling

RARER CAUSES OF ULCERS

Key points

- **Vasculitis can cause cutaneous nodules, livedo, and deep wounds with scalloped borders**
- **Vasculopathic ulcers are often small, painful, and have a background of atrophic blanche**
- **Inflammatory cutaneous conditions, such as pyoderma gangrenosum, may present with ulceration**
- **Chronic ulcers may become malignant**
- **Squamous cell carcinoma can develop in chronic pressure ulcers, venous ulcers, and sites of previous burn injury (ie, Marjolin ulcer).**

Vasculitis

Small-vessel vasculitis may be associated with superficial ulceration. Medium-vessel disease presents more commonly with nodules favoring the lower extremities, livedo reticularis, and deep ulcers with geographic or scalloped borders.⁵⁷

In cryoglobulinemia, ulceration indicates larger vessel involvement⁵⁷ and poor prognosis.⁵⁸ Mixed

cryoglobulinemia has high rates of ulceration, ranging from 11% to 24%.⁵⁹⁻⁶¹ In granulomatosis with polyangiitis—formerly known as Wegener disease—ulcers are pyoderma gangrenosum (PG) –like and often form after minor trauma.⁶²⁻⁶⁴ Ulcers are less common in Churg–Strauss syndrome and microscopic polyangiitis (MPA).^{62,63}

Cutaneous medium-vessel vasculitis, such as polyarteritis nodosa (PAN), manifests as painful nodules on the lower extremities near the malleoli with livedo reticularis and ulceration.^{62,63} A 420-patient study examining patients with PAN and MPA revealed ulceration in 4% of patients with PAN and 6% of patients with MPA.⁶⁵ Ulceration may be more common in purely cutaneous disease.⁶⁶

Vasculopathy

Primary and secondary coagulopathies (Table VI) can cause ulcers because of poor tissue perfusion. The most common hypercoagulable disorder is factor V Leiden deficiency, which can be found in ≤25% of patients with VLUs.⁶⁷ Other important causes of vasculopathic ulcers are discussed in Table VII.⁶⁸⁻⁸⁶

Table VI. Primary and secondary coagulopathies

Causes of primary coagulopathy	Causes of secondary coagulopathy
Factor V Leiden	Hospitalization
Prothrombin G20210A mutation	Trauma
Methyltetrahydrofolate reductase mutation	Surgery
Cystathione-beta-synthase mutation (homocysteinemia)	Immobilization
Antithrombin III deficiency	Obesity
Protein C and S deficiency	Malignancy
Dysfibrinogenemia	Medication
Plasminogen deficiency	Smoking
Elevated factors VIII, IX, or X	Pregnancy
Tissue factor pathway inhibitor deficiency	Antiphospholipid antibody syndrome (screen with anticardiolipin antibodies [IgG, IgA, IgM], anti-beta2-glycoprotein antibodies [IgG, IgM], and lupus anticoagulant)
	Acquired hyperhomocysteinemia

IgA, Immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

Necrobiosis lipoidica

Necrobiosis lipoidica is an idiopathic cutaneous palisading granulomatous condition that is more commonly seen in women and patients with diabetes^{87,88} in the third or fourth decade⁸⁷ of life. It ulcerates 30% to 35% of the time.^{87,89} Well-circumscribed papules and nodules coalesce into larger telangiectatic, violaceous plaques with central red-brown to yellow-brown discoloration. Central areas are atrophic, waxy, and may ulcerate. Lesions are most often on the lower extremities and can be painful⁹⁰ (Fig 6).

Pyoderma gangrenosum

PG is a rare, ulcerating, neutrophilic dermatosis. Inflammatory bowel disease is present in 20% to 30% of patients with PG.^{91,92} Other associated conditions include monoclonal gammopathy, hematologic malignancy, paraproteinemia, Behçet disease, Sweet syndrome, hepatitis, HIV, and systemic lupus erythematosus.⁹³ Lesions begin as tender nodules, plaques, or pustules that become painful ulcers with undermined, violaceous borders and friable wound beds. Cribriform, atrophic scarring results. Ulcers are typically multiple, demonstrate pathergy (induction after trauma), and are usually located on the lower extremities, though they may be peristomal.⁹²

Malignancy-associated ulceration

Squamous cell carcinoma (SCC) can develop in chronic wounds (ie, Marjolin ulcer).⁹⁴ Suspicious features include vegetative or nodular ulcers, elevated or indurated margins, a tendency to bleed, and failure to heal⁹⁵ (Fig 7). In 66 patients with SCC developing in burned or irradiated skin, the mean time from injury to SCC diagnosis was 37 years, with a high recurrence rate (58%) and a 5-year survival rate of 52%.⁹⁶ Malignancy may complicate ulcers of

other etiologies, including VLUs.⁹⁷ Other skin cancers that may present as nonhealing ulcers include basal cell carcinoma, leiomyosarcoma, malignant fibrous sarcoma, Kaposi sarcoma, Merkel cell carcinoma, melanoma, large cell transformation of mycosis fungoides, CD3⁺ cutaneous large T-cell lymphoma, and CD30⁺ anaplastic large cell lymphoma.⁹⁸⁻¹⁰⁶

Hypertensive ulcers

Hypertensive ulcers were described by Martorell in 1945.¹⁰⁷ A later series described 40 patients with ulcers ranging in size from <1 cm to 13 × 27 cm with >50% initiated by trauma.¹⁰⁸ Hypertensive ulcers are painful, with a predilection for the anterolateral lower two-thirds of the leg, and they occur when blood pressure is poorly controlled. They may involve the Achilles tendon^{109,110} and possess a necrotic base with or without satellite lesions.¹⁰⁸⁻¹¹⁰ Poor vasodilation¹⁰⁹ and arteriosclerosis of small and medium vessels are likely contributors. Occlusive arterial disease must be ruled out. Clinically, they can be difficult to distinguish from PG, but obtaining and reviewing a deep biopsy specimen (including the vessels) is diagnostic, and reveals arteriolosclerosis with or without medial calcification.

CHRONIC ULCER WORK-UP

An adequate history and physical examination may point to a diagnosis or guide a physician in choosing the appropriate diagnostic protocol.

Key points

- The initial ulcer evaluation must include a thorough history of present illness, medical history, and a review of systems with a goal of identifying complicating comorbid conditions

Table VII. Important vasculopathic causes of ulceration

Vasculopathy	Patient characterization	Etiology	Presentation
Cholesterol emboli ^{68,69}	Patients are more commonly elderly men with hypertension and atherosclerosis ⁷⁰ ; cholesterol emboli involve skin in 34–35% of cases, ^{70,71} with nearly 20% of cutaneous involvement demonstrating ulceration ⁷⁰	Emboli are triggered by intravascular radiologic intervention, vascular surgery, and anticoagulation ⁷²	In addition to ulceration, cutaneous findings include livedo reticularis, gangrene, cyanosis, nodules, and purpura ⁷¹
Calciphylaxis	1–5% of patients on dialysis ^{73,74} ; risk factors include end stage renal disease, secondary hyperparathyroidism, hypoalbuminemia, and anticoagulation ^{73,75} ; mortality is ≤80% when ulceration occurs ⁷⁶	Demonstrates calcification of medium-sized arteries, leading to cutaneous necrosis ⁷⁵ ; etiology is poorly understood overall	Lesions begin as mottled, violaceous, indurated plaques resembling livedo reticularis and progress to ulcers with deep eschar formation and refractory pain ⁷³
Warfarin-induced necrosis	Usually occurs in patients heterozygous for protein C or S mutations ^{67,77} ; obese individuals are at higher risk	Paradoxical hypercoagulability because of the vitamin K-dependence of proteins C and S ⁷⁷ ; onset is usually 3–5 days after the initiation of warfarin, usually at high doses and without heparinization	Produces petechiae and ecchymoses that progress to hemorrhagic bullae and eventually eschar and ulceration ^{77–79} ; commonly affects the breasts, buttocks, abdomen, thighs and calves ^{78,79}
Livedoid vasculopathy	Female predominance of 3:1 ⁸⁰ ; mean age of onset is 45 years ⁸⁰	Occlusive disease of superficial cutaneous vessels ⁸¹ ; hypercoagulability likely plays a role, ^{80,82} because anticoagulation has led to improvement in multiple cases ^{83–85} ; poor peripheral vascular endothelial function may contribute ⁸⁶	Classic triad of livedo racemosa, episodic and painful purpuric macules and ulcers at the ankles and posterior feet extending to the posterior legs, and stellate porcelain white scars (atrophie blanche) ^{80–82} ; prodromal burning and lack of systemic findings is typical (Fig 5)



Fig 5. Livedoid vasculopathy. This painful ulcer caused by livedoid vasculopathy shows the classic finding of stellate, porcelain white scars (atrophie blanche). (Courtesy of Jennifer Gloekner-Powers, MD.)



Fig 6. Necrobiosis lipoidica. Note the large, well-defined pink-brown plaque with multiple central areas that feature atrophy and ulceration. (Courtesy of Lana Kashlan, MD.)

- **The physical examination may reveal identifying ulcer characteristics and associated skin changes that point to a specific diagnosis**
- **Adjunctive diagnostic testing may be useful and includes obtaining a biopsy specimen, laboratory analysis, and imaging studies**

History of present illness

A patient's medical history can often give a clue as to ulcer etiology. Evaluation of a chronic ulcer



Fig 7. Squamous cell carcinoma. This woman in her 60s presented with a nonhealing ulcer of >12 months' duration. The biopsy specimen revealed invasive squamous cell carcinoma. (Courtesy of Tania J. Phillips, MD.)

should include a thorough history, including time of onset, presence of inciting trauma, progress of healing, history of similar lesions, wound location, and associated symptoms and signs, such as anesthesia, pain, or exudate. For example, ulcers caused by PG often begin or worsen after trauma, starting as a pustule, which rapidly enlarges. Wound care practices and attempted treatments should be noted. In many cases, poor healing is related to inadequate wound care or a lack of compression.

Medical and medication history

A patient's medical history is helpful in elucidating the ulcer diagnosis. Current and previous medications should be carefully reviewed, including chemotherapeutic agents and immunosuppressant drugs. In addition to conditions listed in [Table VIII](#), malignancy should be considered as a primary or secondary cause of ulceration, especially if the wound is of long duration.

Family and social history

Family history of thromboses indicates the risk of a hypercoagulable state; a rheumatologic family history may suggest an autoimmune cause of an ulcer. Occupations involving long hours of standing worsen risk for CVI. Recent travel may point to an infectious etiology. The use of alcohol or drugs contributes to poor nutritional status. Intravenous drug use increases the risk of hepatitis C, which is commonly associated with mixed cryoglobulinemia. Eating habits and a history of smoking raise

Table VIII. Relevant medical history and review of systems screening for chronic ulcer evaluation

Relevant medical history

Cardiovascular: hypertension (controlled or uncontrolled), atherosclerosis, intermittent claudication, congestive heart failure, deep venous thrombosis, vascular malformation, lymphedema, and venous insufficiency

Respiratory: sarcoidosis

Gastrointestinal: inflammatory bowel disease

Hematologic/lymphatic: coagulopathy, recent anticoagulation therapy, blood disorders including: sickle cell anemia, polycythemia vera, thalassemia, and thrombocytopenia

Renal: chronic kidney insufficiency or failure, hemodialysis

Neurologic: disease-causing neuropathy, multiple sclerosis

Musculoskeletal: history of lower extremity trauma or surgery

Psychologic: substance abuse, neurodermatoses, dementia

Endocrinologic: diabetes mellitus and associated complications (retinopathy, nephropathy, neuropathy), corticosteroid excess, thyroid disease

Skin: history of any chronic skin conditions, including vasculitis, necrobiosis lipoidica, sarcoidosis, PG, cutaneous malignancy

Immunologic and rheumatologic: systemic lupus erythematosus, rheumatoid arthritis, Sjögren syndrome, scleroderma, systemic and cutaneous vasculitis

Infection: chronic bacterial, viral, or fungal infections, including HIV, hepatitis, tuberculosis, or other atypical mycobacterial infection

Surgical history: cardiovascular reperfusion interventions

Review of systems

Constitutional: fever, chills, sweats, weight loss or loss of appetite, recent hospitalization

Cardiovascular: chest pain, lower extremity pain with or without exertion, lower extremity pain exacerbated by long periods of standing or worse at the end of the day, lower extremity edema, lower extremity pain worsened with leg elevation

Respiratory: shortness of breath, cough (breathlessness may also indicate cardiac failure)

Gastrointestinal: abdominal pain, nausea, vomiting, diarrhea, bloody stool, constipation

Hematologic/lymphatic: slow healing, tendency to bleed or bruise

Neurological: headaches, lower extremity numbness, burning, tingling or pain

Musculoskeletal: myalgias, arthralgias, recent trauma

Skin: rashes, pruritus, unusual lesions or moles

Eyes: blurred or double vision, decreased visual acuity

awareness for nutritional deficiencies, arterial ulcers, and thromboangiitis obliterans. The patient's living situation and support network can give insight as to whether proper wound care is being carried out.

Review of systems

A review of systems is helpful in identifying systemic conditions that may cause or exacerbate an ulcer (**Table VIII**).

Physical examination

The patient's general appearance, including obesity, should be observed. A clinical examination may reveal systemic disease associated with cutaneous ulceration, such as connective tissue disease or cutaneous malignancy. Helpful features of a physical examination include the following:

- What is the location, size, demarcation, and shape of the ulcer, and is it singular or multiple? Venous ulcers are commonly located in the gaiter

area. Ulcers on the foot or high on the leg are unlikely to be venous. Arterial ulcers tend to be distal. Factitial ulcers often have an angular shape, while vasculitic ulcers often have a punched out appearance.

- Wound edge, color, wound bed characteristics, and the presence of undermining, satellites, or nodularity should be noted. Ulcers in a linear sporotrichoid distribution are suspicious for deep fungal infection, while deeply undermined ulcers with a violaceous border are classically seen in patients with PG.
- Fibrinous, granulation, and necrotic tissue should be documented. Venous ulcers are not necrotic unless arterial disease coexists.
- Lymph nodes should be evaluated and lower extremities examined for coolness or warmth.
- Dorsalis pedis and posterior tibialis pulses must be palpated and peripheral sensation evaluated.

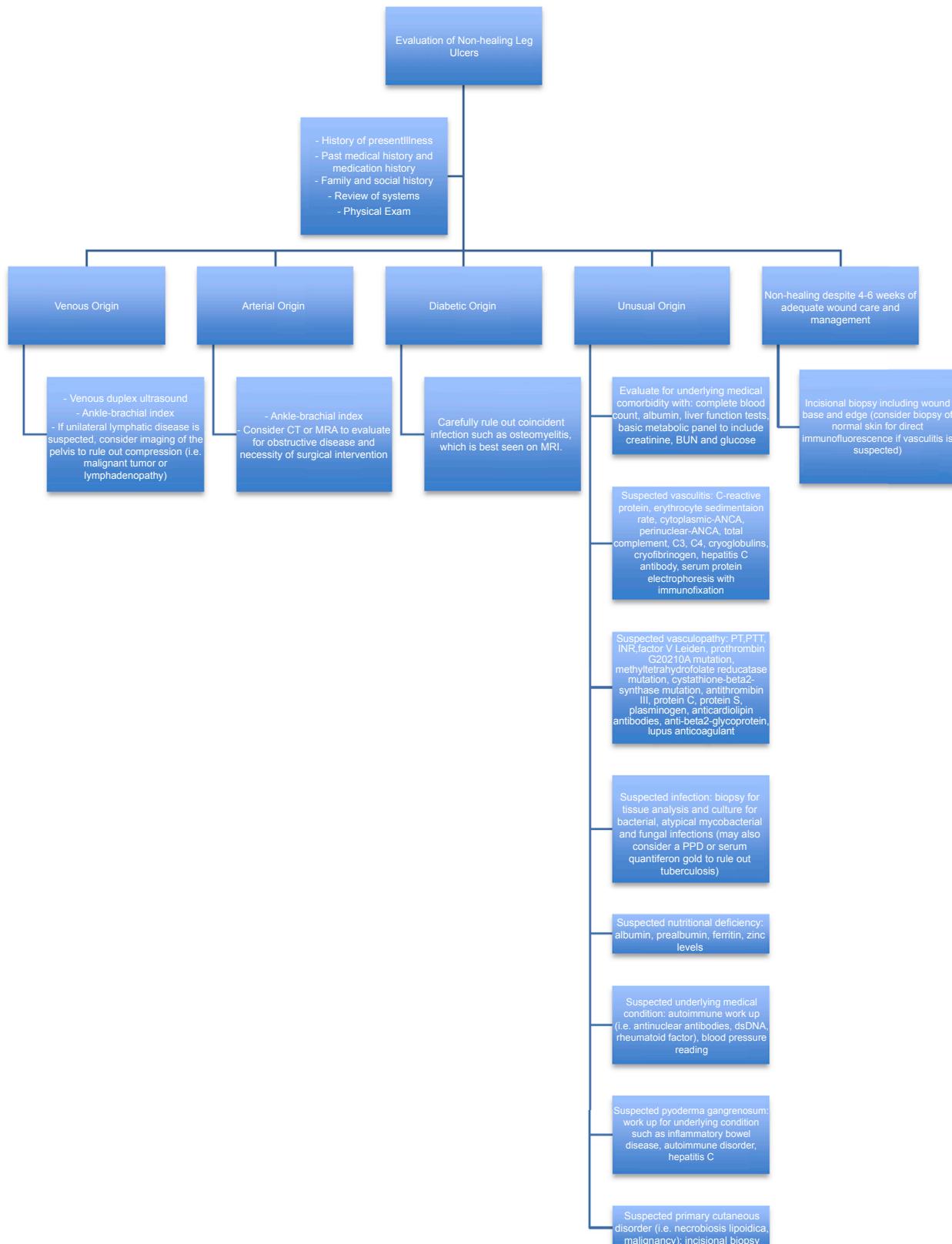


Fig 8. Flow chart for the evaluation of chronic ulcers after collecting a history of present illness, medical history, review of systems, and physical examination.

- Where possible, the ABI should be measured at the bedside.
6. Associated skin findings can be informative, including purpura, papules, plaques, nodules, callus, dermatitis, sclerotic or atrophic changes, and scars, including cribriform scarring and atrophe blanche.
 7. Gross morphologic changes may include the inverted champagne bottle appearance of lipodermatosclerosis/chronic venous disease and Charcot foot deformity of diabetes.
 8. If wounds are purulent and feature spreading erythema and warmth, or pain is out of proportion to wound appearance, infection should be considered. Deep infection, such as osteomyelitis in the presence of DFUs, should also be ruled out by probing the wound with a metal probe to determine whether bone is palpable.

Diagnostic tests

Diagnostic tests should be chosen based on the history and physical examination and include obtaining a tissue biopsy specimen, cultures, hematologic laboratory analysis, vascular studies, and imaging (Fig 8).

If an ulcer has been resistant to healing after 4 to 8 weeks of appropriate treatment, obtaining a biopsy specimen should be strongly considered. Tissue analysis may diagnose infection, vasculitis or vasculopathy, inflammatory conditions, malignancy, and hypertensive ulcers. An incisional biopsy specimen is almost always more useful than a small punch biopsy specimen. The sample should include tissue from the wound bed and normal surrounding tissue. A portion of tissue may be sent for bacterial, atypical mycobacterial, and fungal cultures. If vasculitis is suspected, lesional and perilesional normal skin adjacent to the lesion should be sent for immunofluorescent studies.

Useful laboratory studies include a complete blood cell count to evaluate for anemia and serum protein, albumin, prealbumin, zinc, and ferritin to evaluate for nutritional deficiencies. A basic metabolic panel and liver function tests may also indicate underlying comorbidities.

In patients with suspected vasculitis, C-reactive protein level, erythrocyte sedimentation rate, cytoplasmic antineutrophilic cytoplasmic antibodies, perinuclear antineutrophilic cytoplasmic antibodies, total complement (CH100 or CH50), C3, C4, blood urea nitrogen, and creatinine assessments

are informative. Consider cryoglobulins, cryofibrinogen, hepatitis C antibody, and serum protein electrophoresis with immunofixation to assess for paraproteinemia. When coagulopathy is suspected, a thorough laboratory work-up is essential (Table VI), including prothrombin time, partial thromboplastin time, and international normalized ratio. When an immunosuppressed state is suspected, hepatitis work-up and an analysis for HIV are important. Purified protein derivative or QuantiFERON-Gold tests can be used when there is suspicion for tuberculosis.

The ABI can be performed at the bedside to exclude arterial disease in any patient who needs compression therapy. Segmental pressures, pulse volume recordings, or toe-brachial pressure indices can be performed in the vascular laboratory where bedside testing is not possible because of edema or other factors. Venous duplex Doppler ultrasonographic studies may confirm CVI. Computed tomographic angiography or magnetic resonance angiography can be considered if arteriovenous malformation or obstructive arterial disease that may require surgical revascularization are suspected. If there is suspicion for lymphatic disease, a computed tomography scan of the pelvis to rule out lymphadenopathy or other obstructive pathology may be necessary.

In conclusion, dermatologists may be presented with difficult to heal chronic wounds of unclear etiology. Understanding the pathophysiology of wound healing and the broad differential diagnosis for ulcers is invaluable in arriving at an appropriate diagnosis.

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Wound healing and treating wounds

Chronic wound care and management

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Learning objectives

After completing this learning activity, participants should be able to select appropriate wound care dressings; select appropriate adjunctive topical therapeutics; and select wound-specific therapies for decubitus, venous, diabetic, arterial, rheumatologic, and malignant chronic wounds.

Disclosures

Editors

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In the United States, chronic ulcers—including decubitus, vascular, inflammatory, and rheumatologic subtypes—affect >6 million people, with increasing numbers anticipated in our growing elderly and diabetic populations. These wounds cause significant morbidity and mortality and lead to significant medical costs. Preventative and treatment measures include disease-specific approaches and the use of moisture retentive dressings and adjunctive topical therapies to promote healing. In this article, we discuss recent advances in wound care technology and current management guidelines for the treatment of wounds and ulcers. (J Am Acad Dermatol 2016;74:607-25.)

INTRODUCTION

In the United States, chronic wounds affect >6 million people, with increasing numbers anticipated because of our aging population and the high prevalence of diabetes mellitus. A 2004 analysis found that chronic wounds are the largest direct medical cost center of all human skin diseases, costing \$9.7 billion in the United States in 1 year alone.¹ Chronic wounds can impact quality of life as profoundly as renal and heart disease.² Mortality for some patients with chronic wounds now rivals that of cancer patients.³

Healing wounds is historically one of the most basic and essential practices of human civilization. From Egyptian papyri to the battlefields of Crimea,

there are accounts of wound care from preventing infection to creating bandages and homemade dressings with honey, grease, and lint.⁴ Today, there is a growing body of literature to inform these and more technologically advanced practices.

Once the underlying disease has been addressed (see part I of this 2-part continuing medical education article and Table I), wound bed preparation is a critical concept. Chronic wounds tend to be stuck in the inflammatory phase of wound healing.⁵ To optimize wound healing, the wound should be clean, with a healthy granulating base, and free of infection. Dressings should be chosen to keep the wound moist but not too wet or too dry. If the wound fails to heal after addressing these issues, advanced

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technologies can be considered. Tissue, infection, moisture imbalance, and edge advancement (TIME), which addresses important barriers to wound healing, was developed in 2002 by a wound care consensus group.⁶ We advocate following TIME guidelines for the treatment of chronic wounds.

TISSUE

Key points

- Removal of devitalized tissue is essential for wound healing to occur.
- Debridement, which facilitates removal of this devitalized tissue, can be accomplished using surgical, mechanical, autolytic, enzymatic, and biologic techniques.

Debridement

Debridement or removal of nonviable wound tissue is essential to good wound bed preparation (Table II). Necrotic tissue found in chronic wounds can impair healing and impede keratinocyte migration over the wound bed. Debridement can be performed using surgical, autolytic, enzymatic, biologic, or mechanical methods. A 2013 study reviewing a variety of chronic wound types found that frequent surgical debridement facilitated healing.⁷

Before debridement, a vascular assessment should be performed, especially for ulcers on the lower leg or foot. Surgical debridement must be avoided in ischemic limbs and heel ulcers that are close to bone.⁸ Surgical debridement can be performed with scissors, scalpel, or curette, under topical, local, or general anesthesia. Patients with peripheral neuropathy may not require any anesthesia. Surgical debridement is rapid and effective but can sometimes damage viable tissue. Autolytic debridement occurs when a wound is kept moist, allowing endogenous enzymes (eg, matrix metalloproteinases) to degrade nonviable material from the wound bed. This is slow but less painful and more selective than surgical debridement.

Collagenase is the only commercially available enzymatic debriding agent in the United States. Collagenase ointment (250 units/g) is derived from the bacterium *Clostridium histolyticum* and is most effective for dry wounds with fibrinous slough lacking good granulation tissue, especially when surgical methods are not ideal. In vivo studies have shown that collagenase increases endothelial cell and keratinocyte migration.⁹ Enzymatic debriding agents are an effective alternative for removing necrotic material from pressure ulcers, leg ulcers, and partial-thickness wounds.¹⁰⁻¹² Biologic debridement using medical grade maggots is a rapid and efficient debridement modality usually reserved for

Key strategies	Tissue	Infection	Moisture balance	Wound edge advancement
Debridement (surgical, mechanical, or autolytic); medical grade honey; moisture-retentive dressings (enzymatic and collagenase); biologic	Removal of necrotic and/or devitalized tissue and fibrinous slough	Recognition of wounds at high risk of infection, malodor, delayed healing, pain, excessive exudate, undermining borders, and friable tissue; prevention and treatment of wound infection	Ensure adequate moisture of wound bed and eliminate excess exudate	Create a wound bed microenvironment that promotes healing at the cellular level

Biologic dressings (epidermal—Epicel; dermal—Biobrane, Integra, Oasis, Dermagraft; combination—Apligraf); topical becaplermin; horse chestnut seed extract; Vasculera; hyperbaric oxygen therapy; and hydrotherapy

Table II. Methods of debridement

Type of debridement	Approaches	Clinical context
Surgical	Removal of tissue with scissors and scalpel	Should be performed by a skilled practitioner only, faster results, may require local anesthesia, often needed for diabetic foot wounds, and should be avoided in ischemic limbs and heel ulcers
Mechanical	Saline gauze—"wet to dry" dressings Hydrotherapy: pulsed lavage, whirlpool debridement, debridement pads with monofilaments, ultrasonographic debridement, and atomized saline	Less painful than surgical but may harm viable tissue
Autolytic	Endogenous enzymes (eg, proteolytic, fibrinolytic, and collagenolytic) interact with moisture retentive dressings; medical grade manuka honey (via osmosis)	Pain-free, "selective"; slower than other methods (improvement in 72 hours); avoid in septic or immunocompromised patients
Enzymatic	Collagenase ointment; discontinued (eg, papain, streptokinase, and fibrinolysin-desoxyribonuclease)	Faster than autolytic; selective, easy to use; may crosshatch over eschar with no. 15 or 11 blade; avoid silver dressings; okay to use with infected wounds or on patients taking anticoagulants, but may cause allergy/stinging
Biologic	Larval therapy: <i>Lucilia sericata</i> , <i>Phaenicia sericata</i> , and <i>Lucilia cuprina</i>	May require patient coaching and can be painful

recalcitrant fibrinous wounds. The powerful enzymes in their saliva dissolve necrotic tissue, which the maggots ingest. This modality is infrequently used in the United States because of the associated pain and patient and provider reticence.¹³ A recent randomized controlled trial found that subjects treated with larvae experience more discomfort than subjects treated with hydrogel dressings.¹⁴

Mechanical debridement can be accomplished using a variety of modalities, including wet to dry dressings, irrigation of wounds with hydrosurgery, ultrasonography, or high pressure wound irrigation. These methods are nonselective and can be painful.

INFECTION

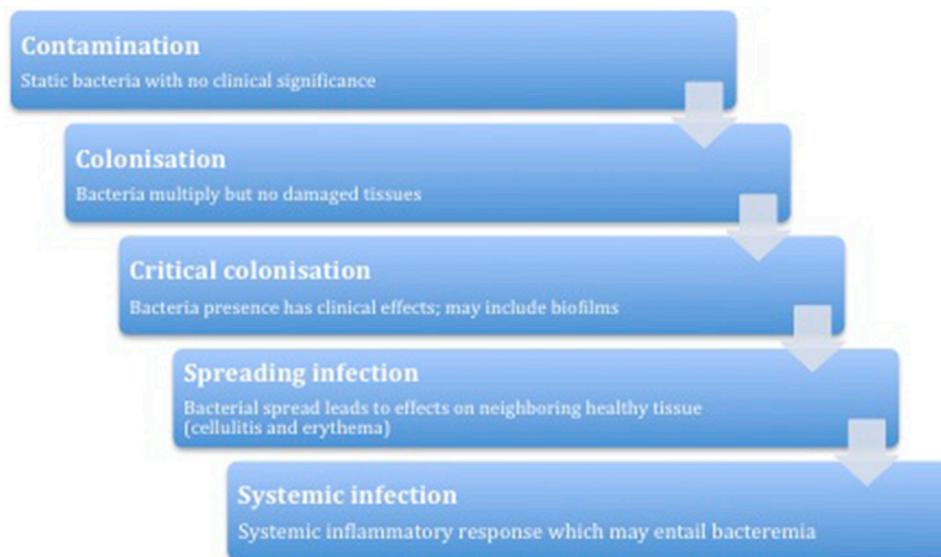
Key points

- Addressing local infection using cleansing agents and topical antimicrobials can improve healing
- Cadexomer iodine has antimicrobial activity and is helpful in healing chronic venous ulcers and decubitus ulcers
- Dilute vinegar topical soaks may reduce recurrent bacterial colonization in chronic wounds, especially for *pseudomonas*
- In frequently infected wounds or those at high risk, silver-impregnated dressings may be given a two-week trial period for efficacy.
- For deep infection, systemic treatment is required.

In chronic wounds, bacteria may colonize the wound without impairing the healing process (colonization). As the bacterial load increases to critical colonization, wound healing becomes impaired (local wound infection). Infection may spread into surrounding tissues, resulting in deep infection, which may progress to systemic infection (Fig 1). Infection may present as delayed healing, increased exudate, malodorous discharge, undermined borders, friable tissue, increasing wound size, increased pain, and new areas of slough (Table III).¹⁵ Addressing local wound infection using cleansing agents and topical antimicrobials can improve healing. For deep or systemic infection, systemic treatment is required.

Cleansing

Wounds can be cleaned with either normal saline or tap water.¹⁶⁻¹⁸ Detergents, hydrogen peroxide, and concentrated povidone-iodine solutions should be avoided because of tissue damage and toxicity.¹⁹⁻²¹ Cleansing wounds in dilute vinegar 0.5% acetic acid can have significant antimicrobial effects, particularly in chronic wounds that are prone to frequent infection with *Pseudomonas aeruginosa* (Fig 2).²² One study found that a 10-minute soak with 0.5% acetic acid is bactericidal against Gram-positive and -negative isolates from wounds.²³ This should be used for short periods of time until the wound is clean.

**Fig 1.** Chronic wound infection continuum.**Table III.** Infection in chronic wounds

Systemic signs of infection	Local signs of infection
Malaise, anorexia, fever, and chills	Poor healing, rapid increase in wound size, increased fibrinous coverage, increased friable granulation tissue, increased wound exudate, malodor, increased pain or tenderness to palpation, and frank pus or abscess formation

Antimicrobial agents

Topical antimicrobials are preferred over systemic antimicrobials for superficially infected wounds given direct targeting of the bacterial burden and the concern for development of resistance with systemic treatments. However, bacterial resistance to topical agents can occur, and they should be discontinued once the wound is clean.⁶ Topical antibiotics, such as gentamicin and neomycin, frequently cause allergic contact dermatitis in chronic wounds and should be avoided.²⁴ They offer no benefit in the rate of infection or healing time in surgical wounds compared to petroleum jelly.²⁴⁻²⁶ While concentrated povidone iodine is cytotoxic, low concentrations have broad-spectrum antimicrobial activity without inhibiting cell growth. Cadexomer iodine is compounded into gel beads that release low concentrations of iodine into the wound over time. This is bactericidal against some resistant strains of bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA),²⁷ and may

**Fig 2.** Dilute vinegar preparation (0.5% acetic acid soak).

improve the healing of chronic venous leg ulcers (VLU) and decubitus ulcers.^{28,29}

Topical metronidazole gel has been shown in 3 randomized controlled trials to be effective at reducing malodor in fungating malignant wounds or sites prone to anaerobic growth.³⁰⁻³²

Silver is thought to bind to bacterial cell membranes, interfere with bacterial electron transport, bind to bacterial DNA, and bind up key building blocks in the cell. It is toxic to bacteria, including MRSA, and fungi in vitro. The 2012 international consensus guidelines on the use of silver-containing products recommend that silver dressings be used for wounds that are infected or at high risk of becoming infected for a 2-week trial period. If a silver dressing proves to be insufficient after 2 weeks, more aggressive therapies, such as systemic antibiotics, may be indicated.³³ A meta-analysis of randomized controlled trials that included both infected and infection-free chronic ulcers has shown that silver-impregnated dressings are superior to non-silver dressings in reducing wound size, but the data

for complete wound healing and healing rate are more equivocal.^{34,35}

Medical grade manuka honey from New Zealand and Australia is thought to have both peroxide and nonperoxide antibacterial activity that can inhibit >50 species of bacteria.³⁶ Manuka honey is available both as a topical preparation or honey-impregnated dressings (MediHoney; Derma Sciences, Princeton, NJ). A recent Cochrane review discussed low-quality evidence showing quicker healing of partial-thickness burns compared to conventional treatments and infected postoperative wounds more quickly than antiseptics and gauze.³⁷

Topical agents can reduce superficial wound infection, but systemic antibiotics should be used in patients with deep or systemic infection.

MOISTURE BALANCE

Key points

- Adequate moisture balance promotes keratinocyte migration and wound healing
- A dressing that will keep the wound moist but not too wet or too dry should be chosen
- While there are multiple types of moisture retentive dressings, the 5 basic categories are films, foams, hydrocolloids, alginates, and hydrogels
- Negative pressure therapy appears to be effective in postsurgical wounds.

Moisture-retentive dressings

Moisture balance entails selecting the appropriate dressing to absorb exudate yet keep the wound moist. There are a wide variety of wound dressings, ranging from over the counter adhesive bandages to complex biologic dressings engineered with neonatal keratinocytes.

Moisture-retentive dressings (MRDs) have moisture vapor transmission rates (MVTRs) of <35 g/m²/hr to allow for moist wound healing. For acute wounds, the benefits of MRDs have been clearly proven in clinical trials.³⁸ A systematic review of 99 studies on MRDs also showed their clinical benefit in chronic wounds.³⁹ Initial healing rates with these dressings plus compression is faster than compression alone in venous ulcers.⁴⁰ These dressings are also cost effective in chronic VLU care considering all factors (eg, cost for materials, nursing, and travel time).⁴¹

The 5 basic types of MRDs are films, foams, hydrocolloids, alginates, and hydrogels (Table IV). Films are thin, elastic transparent sheets of polyurethane that adhere with acrylic to skin but are gas permeable. Films are the choice dressing for donor sites of split-thickness skin grafts and may also be

used in acute surgical wounds.⁴² Foams are bilaminate dressings composed of hydrophobic polyurethane foam sheets with a hydrophilic surface to prevent leakage and bacterial contamination. These can provide padding over bony prominences⁴³ and are suitable for mild to moderately exudative wounds. The removal of foam dressings may require soaking with saline solution if the wound is not very exudative.⁴³

Hydrocolloids are soft conformable dressings composed of an adhesive matrix containing carboxymethylcellulose, pectin, and gelatin attached to a foam or polyurethane film backing. Wound exudate interacts with the hydrocolloid to form a yellow gel, promoting autolytic debridement. These dressings conform well, allowing for easy adoption by patients, and they are helpful for wounds with mild amounts of exudate. Because they are waterproof they can be worn while bathing or swimming but may create maceration around the edges. In several meta-analyses, wounds treated with hydrocolloid dressings showed statistically significant improvement compared to sterile gauze.⁴⁴⁻⁴⁷ Hydrocolloids should be applied with generous margins to avoid rolling corners and, once placed securely, may be left for 2 to 4 days. To avoid maceration, a layer of petroleum jelly or zinc oxide paste can be applied around the wound margins.

Alginates are highly absorbent dressings comprised of cellulose-like polysaccharides derived from algae or kelp. They can exchange calcium for sodium to absorb fluid and also have hemostatic properties. They are dry fluffy sheets that become moist as they absorb drainage.⁴⁸ Alginates are ideal for heavily exudative wounds and should not be used for dry or minimally exuding wounds.⁴⁹

Hydrogels are composed of 96% water inside a cross-linked hydrophilic polymer network. They are available as liquid gels, which can be squirted into a wound, or as sheets that can be placed on the wound surface. They are best suited for dry, necrotic wounds. They can be cooling and soothing for patients, especially if the wound is painful.⁵⁰

Dressing placement

Some dressings are adherent, such as hydrocolloids and films; others require a secondary dressing to keep them in place. This can be accomplished with a gauze wrap followed by an elastic compression wrap, such as an ACE or Coban bandage (3M, Minneapolis, MN). If more compression is desired, an Unna boot or multilayer compression wrap (Fig 3) can be used.⁵¹ Unna boots have zinc oxide impregnated into rolled gauze that can be applied with the knee flexed and wrapped tightly, overlapping each

Table IV. Moisture-retentive dressings by type

Dressing type	Description	Advantages	Disadvantages	Brand-names
Hydrocolloids	Malleable sheets comprised of waterproof gels or foams within polyurethane films; excellent for mildly exudative wounds	Stimulates granulation tissue, simple to apply, and waterproof	Gel formation, drainage, and not largely suitable for cavities	Duoderm (Convatec), NuDerm (Johnson & Johnson Medical), Comfeel (Coloplast Sween, Inc), Hydrocol (Dow Hickam), Cutinova (Smith & Nephew), Replicare (Smith & Nephew United), and Tegasorb (3M)
Alginites	Consists of polysaccharides derived from kelp and algae; ideal for highly exudative wounds	Absorbent, confers hemostatic benefits, and suitable for use in sinuses	Not appropriate for dry wounds—may cause pain with dressing removal if too dry; can require frequent dressings changes for wounds with significant drainage	Algiderm (Bard), Algisite (Smith & Nephew), Algisorb (Covidien-Vestal), Algosteril (Johnson & Johnson Medical), Kaltostat (Convatec), Curasorb (The Kendall Co), Sorbsan (Dow Hickam), Melgisorb (Mölnlycke Health Care), SeaSorb (Coloplast), and Kalginate (DeRoyal)
Hydrogels	Cross-linked hydrophilic polymer holding significant amount of water; excellent for dry, necrotic wounds	Stimulates autolytic debridement and comfortable for the patient	Can result in skin maceration if wound is highly exudative	Vigilon (CR Bard), Nu-gel (Johnson & Johnson Medical), Tegagel (3M), FlexiGel (Smith & Nephew), Curasyn (The Kendall Co), Clearsite (Conmed Corp), Curafil (The Kendall Co), Curasol (The Kendall Co), Carrasyn (Carrington Laboratories), Elasto-Gel (SW Technologies), Hypergel (Scott Health Care), Normgel (SCA Hygiene Products), 2nd Skin (Spenco Medical, Ltd), and Transigel (Smith & Nephew)
Films	Thin layers of elastic polyurethane; used for donor sites for split-thickness skin grafts	Provides barrier against bacteria, permeable to gases, and allows for visualization of the wound	Poor drainage of fluid, and removal may be potentially damaging to newly formed epithelium	Tegaderm (3M Healthcare), Polyskin II (Kendall Healthcare), Bioclusive (Johnson & Johnson Medical), Blisterfilm (The Kendall Co), Omniderm (Omnikron Scientific Ltd), Proclude (Convatec), Mefilm (Mölnlycke Health Care), Carrafil (Carrington Lab), and Transeal (DeRoyal)

Bilaminate dressings with hydrophobic polyurethane foam sheets with a hydrophilic surface; ideal for wounds over bony surfaces, in body cavities, and mild to moderately exudative wounds

Absorbs and retains moisture, prevents leakage of drainage and bacterial contamination, and easily shaped to accommodate site of wound

Can become adherent if drainage dries

Polymem (Ferris Corp), Allevyn (Smith & Nephew United), Biopatch (Johnson & Johnson Medical), Curafoam (The Kendall Co), Flexzan (Dow Hickam), Hydrasorb (Tyco/Kendall Co), Lyofoam (Convatec), and Mepilex (Mölnlycke Health Care)

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Fig 3. Multilayer compression wrap.



Fig 4. Negative pressure therapy on acute wound. (Courtesy of Mary Gloeckner, RN.)

layer by 50% with each turn, to create a smooth, firm compression wrap that ends just below the knee.⁵²

Vacuum-assisted closure

Vacuum-assisted closure, or negative pressure therapy, has been used in chronic wound management, including diabetic foot ulcers (DFUs), pressure ulcers, and in acute wounds, such as traumatic wounds, surgical wounds, and flaps and skin grafts (Fig 4). The exact mechanism of action is unknown, but creation of a moist environment, reduction of edema, reduction in size of the wound, stimulation of angiogenesis, and the formation of granulation tissue have all been attributed to negative pressure therapy.⁵³ One prospective randomized trial found no difference in total bacterial load in wounds treated with vacuum-assisted closure versus conventional moist gauze treatment; however, wounds treated with vacuum had a significant reduction in surface area and increased rate of wound healing.⁵⁴ A Cochrane review suggests that negative pressure therapy may assist wound closure in patients with postoperative diabetic foot wounds compared with moist dressings⁵⁵; other postsurgical wounds may also benefit from negative pressure therapy, but data are insufficient to support general use.⁵⁶

EDGE OF WOUND

Key points

- **Biologic skin substitutes mimic the architecture of normal skin and activate healing cascades within the patient**
- **The 3 main categories of biologic skin substitutes include epidermal, dermal, and dermoepidermal combination constructs.**
- **Hyperbaric oxygen is most helpful in patients with diabetic foot ulcers**
- **Becaplermin gel is approved by the US Food and Drug Administration for the treatment of diabetic foot ulcers**

Advancing the edges of any wound requires addressing not only local but also systemic factors. Reepithelialization requires a well-vascularized wound bed, adequate oxygen and nutrients, control of systemic diseases, such as diabetes mellitus, and treatment of underlying disease, such as chronic venous insufficiency or arterial disease. A variety of devices from biologic dressings to hyperbaric oxygen chambers and chronic disease management should be considered in these patients.

Bioengineered dressings

Since the 1970s, bioengineered dressings have evolved to become a viable adjunct to traditional wound dressings, particularly for hard to heal venous and diabetic wounds. These dressings use human or animal skin components to mimic the architecture of normal skin. Such dressings have yet to replace skin grafts, but they are less traumatic than creating donor sites.⁵⁷ These dressings not only optimize the healing environment by replacing the lost epidermal barrier and creating a moist wound bed but also provide a structural scaffold and release factors that stimulate healing.⁵⁷

Bioengineered dressings may be categorized into 3 groups: epidermal, dermal, and combination dermoepidermal constructs (Table V). The only cultured epidermal autograft that is currently commercially available and has been approved by the US Food and Drug Administration (FDA) is Epicel (Genzyme Corporation, Cambridge, MA). The manufacturer grows autologous keratinocyte cultures obtained from a patient biopsy specimen that become large enough to graft onto the patient within 16 to 21 days.⁵⁸ Epicel has limited clinical use as a “humanitarian use device” only and remains an adjunct to split-thickness grafting in burn wounds.⁵⁹

Dermal constructs are frequently used in both acute and chronic wounds,^{60,61} particularly in burns.⁵⁷ Biobrane (UDL Laboratories, Rockford, IL) is a temporary dressing constructed of a nylon mesh coated

with porcine collagen and newborn human fibroblast cells and bonded to a semipermeable silicone membrane.⁶¹ It is used as a dressing in superficial burns before or in lieu of grafting.⁶⁰ Integra (Integra Life Sciences; Plainsboro, NJ), is a bilayered construct consisting of a matrix of type I bovine collagen and chondroitin-6-sulfate (a glycosaminoglycan from shark cartilage) covered by a temporary silicone epidermal sheet. The pores in the construct allow for migration of a patient's own endothelial cells and fibroblasts. As a wound heals, the silicone sheet is removed and a thin split-thickness autograft is placed.⁶⁰ This dressing is used in partial- to full-thickness burns, in soft tissue reconstruction over exposed tendons, joints, and bone, and in chronic vascular and pressure ulcers. OASIS Matrix (Smith & Nephew, Andover, MA) is derived from porcine small intestinal submucosa and is indicated for use in a variety of wounds, including venous, pressure, diabetic ulcers, and chronic vascular wounds.⁶²⁻⁶⁴

Dermagraft (Organogenesis Inc, Canton, MA) is a dermal matrix composed of metabolically active human fibroblasts from neonatal foreskin seeded onto a bioabsorbable polyglactin mesh scaffold. This biologic dressing is currently approved by the FDA for the treatment of full-thickness DFUs present for >6 weeks and without exposed tendon, muscle, joint capsule, or bone. Dermagraft is supplied as a cryopreserved specimen in a clear bag containing one 2- × 3-in, single-use application and must be stored at -75°C before application.⁶⁵ In a 35-center trial of 314 patients with DFUs, 30% achieved complete wound healing with Dermagraft compared to 18.3% in the control group.⁶⁶ Dermagraft has anecdotally been used for venous ulcers, but it has not approved by the FDA for this indication.⁵⁹

Bilayered skin constructs (BSCs) have been particularly successful in patients with venous and diabetic ulcers. Apligraf (Organogenesis Inc), was the first commercially available product of this nature, containing a layer of differentiated keratinocytes and a synthetic dermis created from bovine type I collagen and human fibroblasts.⁵⁹ Both cell types in this product are generated from human neonatal foreskin. BSC is supplied as a circular disc that is 75 mm in diameter and approximately 0.75-mm thick, and it is easily secured in place over chronic wounds and replaced every few weeks until the ulcer has healed (Fig 5).⁵⁹ In 1 clinical trial of 120 patients with VLUs present for >12 months, 47% of BSC patients versus 19% of control patients had complete wound closure after 5 applications.⁶⁷ Similarly, in 208 patients with DFUs, 56% of BSC patients achieved wound healing versus 38% of controls.⁶⁸ Currently, the product is approved by

Table V. Biologic dressings

Type	Description	Uses	Advantages	Disadvantages	Brand name
Epidermal	Cultured epidermal allograft from patient's own skin	Full-thickness burns	Autograft	Expensive, requires advanced ordering, and is a humanitarian use device Adherent to wound and risk of infection	Epicel (Genzyme Corp)
Dermal	Nylon mesh with porcine collagen and human fibroblasts attached to silicone membrane	Superficial burns	Transparent, permitting visualization; different sizes available; pores allow for fluid drainage		Biobrane (UDL Laboratories)
	Bilayered, with matrix of type I bovine collagen and chondroitin-6-sulfate (a glycosaminoglycan from shark cartilage) beneath a silicone epidermal sheet	Partial- and full-thickness chronic ulcers and surgical wounds	Immediately available	Requires a 2-step operation and is expensive	Integra Bilayer Wound Matrix (Integra Life Sciences Corp)
	Matrix derived from porcine small intestine submucosa	Variety of chronic wounds; contraindicated in third-degree burns	Immediately available (2-year shelf life) and applicable to a variety of wound types	Not for use in third-degree burns	OASIS wound matrix (Smith & Nephew)
	Dermal matrix with human fibroblasts seeded onto a bioabsorbable polyglactin mesh scaffold	Full-thickness diabetic foot ulcers	Excellent for diabetic wounds	Must be stored at -75°C until use and is expensive	Dermagraft (Advanced Biohealing, Inc)
Multilayer	Upper epidermal layer with differentiated keratinocytes; lower dermal layer with bovine type I collagen and human fibroblasts	Venous ulcers lasting for >4 weeks and diabetic foot ulcers lasting >3 weeks	Has occlusive properties	Requires advanced ordering, and a specific application is required	Apligraf (Organogenesis, Inc)

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the FDA for the treatment of VLUs of >4 weeks' duration and DFUs of >3 weeks' duration. Anecdotally, it has been used in burns treated with meshed split-thickness autografts,⁶⁹ acute surgical wounds left to heal by secondary intention, and in patients with epidermolysis bullosa, aplasia cutis congenita, polyarteritis nodosa, sarcoidosis, livedo vasculopathy, and pyoderma gangrenosum.⁵⁹

Novel topical approaches

Regranex 0.01% gel (Healthpoint Biotherapeutics, Fort Worth, TX) contains bcaplermin, a recombinant human platelet-derived growth factor, and is approved by the FDA for the treatment of DFUs (Table VI). This topical agent is an option for patients who are not responsive to conservative off-loading and debridement therapy for DFUs. In clinical trials, diabetic wounds treated with platelet-derived growth factors showed a 43% increase in the incidence of complete wound closure compared with placebo gel.⁷³ While the cost is high, the reduction in healing time can make bcaplermin more cost effective.⁷⁴ Postmarketing data suggest that diabetic patients who use >3 tubes of the gel have an increased risk of cancer mortality.⁷⁵

Promogran dressing (Johnson & Johnson, Somerville, NJ) consists of a mixture of collagen and oxidized regenerated cellulose and promotes healing through the inhibition of proteases in the wound microenvironment.^{76,77} A randomized controlled trial found that Promogran was slightly superior to moistened gauze in healing DFUs.⁷⁷ Anecdotally, Promogran has been used in the treatment of venous ulcers, but additional evidence to support more broad clinical use is needed.

Matristem (ACell, Columbia, MD), an extracellular matrix derived from porcine urinary bladder, is available in sheet form and has shown clinical effectiveness in limited case series of open chronic wounds.^{78,79}

Epifix (MiMedX, Marietta, GA) is one of the available amniotic membrane products available as topically applied sheets and is comprised of dehydrated human amnio/chorion membrane allograft with a single layer of epithelial cells, a basement membrane, and an avascular connective tissue matrix.⁸⁰ Clinical uses with chronic wounds are beginning to be explored.

The Cutimed Sorbact dressing (BSN Medical, Hamburg, Germany) provides an innovative approach to reducing wound bioburden. Composed of dialkylcarbamol chloride, it binds bacteria through hydrophobic interactions. The bacteria are subsequently removed with dressing changes.⁸¹



Fig 5. Apligraf on a leg wound.

Hyperbaric oxygen therapy

Hyperbaric oxygen therapy (HBOT) is defined as the use of 100% oxygen at pressures above 1 atmosphere, which enhances oxygen saturation in the blood in the form of oxyhemoglobin.⁸² Hyperoxia promotes wound healing through an increase in growth factors and the production of nitric oxide, which releases endothelial progenitor cells.⁸³ HBOT has been used for chronic wounds, poorly healing wounds, acute wounds, and DFUs. One systematic review found a reduced risk of major amputation and improved wound healing in patients with DFUs who were treated with HBOT therapy.⁸⁴ A recent systematic review found insufficient evidence to support the use of HBOT for acute surgical or traumatic wounds.⁸² The use of HBOT is also limited by the cost of transportation and access to therapy units.

DISEASE-SPECIFIC MEDICAL MANAGEMENT

Key points

- **Compression therapy is the cornerstone of treatment of venous ulcers.**
- **Pressure relief with proper footwear and contact casting, correction of arterial disease, treatment of infection, and wound debridement are mainstays of diabetic foot ulcer treatment.**
- **Frequent repositioning with specialized support surfaces and pressure-reducing mattresses are key interventions in the treatment and prevention of pressure ulcers.**

Table VI. Topical adjuvants

Agent	Classification	Use	Bacterial sensitivity
Metronidazole gel 1%	Topical antibiotic	Odor reduction in malignant or necrotic wounds	Yes
Becaplermin (Regranex)	Recombinant human platelet-derived growth factor	Diabetic foot ulcers	No
Collagenase (Santyl)	Proteolytic enzyme	Promotes debridement and reepithelialization; best for dry wounds	No
Medical grade honey	Topical antimicrobial agent	Antimicrobial properties and autolytic debridement	Yes
Horse chestnut extract	Venodilator	Venous ulcers	No ⁷⁰⁻⁷²
Miltefosine (Miltef)	Antiparasitic	Malignant, fungating ulcers	Antifungal and antiprotozoal
Hyperoxygenated fatty acid cream (Mepentol)	Hyperoxygenated fatty acid preparation	Pressure ulcers	No
Cadexomer iodine	Antimicrobial agent	Venous ulcers	Yes
Topical lidocaine gel 1-2%	Topical anesthetic	Pain reduction in arterial and venous ulcers	No
EMLA 5%	Topical anesthetic	Pain reduction in arterial and venous ulcers	No
Acetic acid 0.5%	Antimicrobial agent	Chronic wounds	Yes
Protease modulating matrix (Promogran)	Protease inhibitor	Diabetic and venous ulcers	No

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EMLA, Eutectic mixture of local anaesthetics.

Disease-specific, medical management of chronic wounds is discussed below. Treatment strategies, their use, and their bacterial sensitivity are shown in Table VII.

Pressure ulcers

Treatment of pressure or decubitus ulcers is aimed at interventions that reduce pressure, shearing forces, friction, and excessive moisture.^{98,99} Underlying disease should be addressed, including nutrition and hydration. The National Pressure Ulcer Advisory Panel states that MRDs are preferred because gauze dressings may stick to wounds, causing pain with dressing changes.^{85,100} Frequent repositioning every 2 hours is one of the core elements of treating and preventing pressure ulcers.^{86,98,99,101} Specialized support surfaces, such as foam or sheepskin pads, pressure-reducing mattresses, and mattress overlays are used to increase the area of pressure distribution, minimizing the risk of ulcer formation.^{87,98} In addition, protection of the wound from incidental soiling with topical skin protectants may help prevent decubitus ulcers that are located on the sacrum.

Venous ulcers

Compression therapy with either graduated compression stockings or compression bandages is the central treatment for venous ulcers.^{90,102,103} A

systematic review in 2012 determined that compression improves rates of healing compared to no compression, that multicomponent devices are superior to single-component devices, and that compression devices with an elastic component may be superior to those inelastic devices.^{90,104-107} Caution should be used with compression treatments in the setting of congestive heart failure, in elderly or frail patients, and in patients with severe arterial disease.¹⁰⁷ Multilayer compression wraps work well when patients are in the active phase of treatment; knee-high compression stockings at 30 mm Hg are best suited to prevent recurrence in patients whose ulcers have healed. Long-term evidence suggests that superficial venous surgery may be beneficial in the prevention of ulcer recurrence in patients with isolated superficial reflux or with mixed superficial and segmental deep reflux.⁹²

There is some evidence to support the use of cadexomer iodine in VLUs to promote healing.²⁸ Topical 5% eutectic mixture of local anesthetics (lidocaine/prilocaine cream) has also been shown in a multicenter, placebo-controlled study to significantly reduce pain associated with debridement of chronic venous and arterial ulcers.¹⁰⁸

Systemic pentoxifylline is a useful adjunctive therapy for venous ulcers.¹⁰⁹ A 2012 Cochrane review found that pentoxifylline—either alone or in combination with compression therapy—improves

Table VII. Evidence for disease-specific medical management

Disease type	Treatment strategies	Description	Studies	Study outcome
Pressure	Avoid gauze dressings	Use moisture-retentive dressings instead	Black et al ⁸⁵	NPUAP consensus conference recommendation
	Reposition every 2 hrs	Reduces pressure on bony prominences	Gillespie et al ⁸⁶	CSR recommendation for intervention
	Support surfaces Topical ointments	Foam pads, Australian sheepskin pads Mepentol, a topical hyperoxygenated fatty acid preparation, applied to ulcer area	McInnes et al ⁸⁷ Torra i Bou et al ¹³²	CSR recommendation for intervention RCT of 331 patients over 30 days compared Mepentol to generic greasy product, demonstrated decreased pressure ulcer incidence
	Revascularization	Bypass surgery around blockages in leg arteries Wet to dry dressings, wound vacuum dressings, debridement, skin grafting, and minor amputations if needed	Bradbury et al ⁸⁸ Chiriano et al ⁸⁹	CSR comparing bypass surgery first or balloon angioplasty Nonrandomized Veterans Affairs study evaluating the success of conservative therapy in patients with documented ABI <0.9 but a transcutaneous oxygen level >30 mm Hg; more than two-thirds of patients healed with conservative therapy. Requiring surgery later did not increase risk of mortality or amputations
Arterial	Conservative therapy		Nelson and Bradley ⁴⁶	CSR recommendation had insufficient evidence to support
	Applied to the ulcer to treat pain		O'Meara et al ⁹⁰	CSR shows improved healing compared to no compression, especially multicomponent systems
	Compression	Improves venous return	Nelson et al ¹³³	CSR shows efficacy compared to no compression; not compared to standard compression devices
	Intermittent pneumatic compression	Improves venous return in a cyclic manner	Palfreyman et al ¹³⁴	CSR suggests hydrocolloid dressings are not more effective than standard low-adherent dressings placed under compression
Venuous	Low-adherent dressings	Often made of padded cotton		CSR suggests some evidence for healing
	Cadexomer iodine	Bacteriocidal and wound cleaning properties	O'Meara S et al ¹³⁵	CSR suggests reduction in pain associated with venous leg ulcers
	Ibuprofen-releasing dressings	Ibuprofen slow-release dressings given for pain	Briggs et al ¹³⁶	compared to standard dressings

Topical EMLA cream	Combination lidocaine 2.5% and prilocaine 2.5%; local anesthetic to treat pain	Briggs M et al ¹³⁶	CSR suggests reduced pain when used during debridement
Bilayered construct	Apligraf	Jones et al ¹³⁷	CSR suggests improved healing time compared to compression alone
Flavonoid-containing compound	Venotonic compounds improve microcirculation defects that contribute to pathology, including micronized purified flavonoid fraction and hydroxyethylrutosides	Scallan et al ¹³⁸	CSR suggests improved healing but studies are biased
Pentoxyfylline	Improves blood flow systemically, theoretically improving venous return	Jull et al ⁹¹	CSR shows efficacy for improved healing, possibly even in the absence of compression
Venous surgery	Various surgical procedures to improve venous insufficiency	Hardy et al ¹³⁹	CSR suggests there may be long-term improvement with use of ligation and valvuloplasty in patients with deep venous incompetence; however, existing evidence is weak
		Barwell et al ⁹²	RCT suggests reduced 12-month ulcer recurrence with superficial ablative surgery in patients with superficial venous insufficiency or mixed superficial and deep venous insufficiency
	Total contact casts, cast walkers, removable shoe modifications (shoes and foot pads)	Lewis and Lipp ⁹³	CSR shows nonremovable, pressure relieving casts are more effective than removable ones, particularly in conjunction with Achilles tendon lengthening
Diabetic	Pressure reduction		Retrospective study suggests reduced rate of amputation in diabetic patients that undergo revascularization
Surgical revascularization	Surgical revascularization to restore bloodflow (including peripheral angioplasty and bypass grafting)	Faglia et al ⁹⁴	RCT suggests improved healing of noninfected diabetic ulcers with Apligraf compared to control treatment
Bilayered construct	Apligraf	Veves et al ⁶⁸	

Continued

Table VII. Cont'd

Disease type	Treatment strategies	Description	Studies	Study outcome
Bioabsorbable membrane with human fibroblasts	Dermagraft	Marston et al ⁶⁶		Randomized, controlled, multicenter study suggests improved healing of chronic diabetic ulcers with dermagraft compared to control treatment
Hyperbaric oxygen	Improves oxygen supply to wounds	Kranke et al ⁸⁴		CSR shows efficacy in the short-term but not long-term healing
Hydrogel dressings	Autolytic debridement	Dumville et al ⁵⁵		CSR shows greater healing as compared to contact dressings
Hydrogel dressings	Autolytic debridement	Edwards & Stapley ¹⁴⁰		CSR endorses efficacy for this intervention
Debridement	Surgical debridement	Tan et al ⁹⁵		Retrospective study suggests early aggressive surgical intervention (including surgical debridement and local limb amputation) reduces the incidence of above the ankle amputations
GC-SFs	Adding GC-SF systemic treatment	Cruciani et al ¹⁴¹		Reduces hospitalization duration and need for amputations per CSR
Negative pressure therapy	Often used in the postoperative setting	Dumville et al ⁵⁵		CSR shows more effective healing in postoperative foot wounds and ulcers
Bevacaplermin gel	Recombinant human platelet-derived growth factor- β	Wieman et al ⁷³		RCT suggests improved healing of chronic diabetic ulcers with application of bevacaplermin gel compared to placebo
Malignant	Miltexine (Miltex), cytostatic agent	Adderley and Smith ⁹⁶ Leonard et al ⁹⁷		CSR for intervention RCT showing efficacy in breast cancer patients in multicenter study
Foam dressings with silver	Work to reduce odor	Adderley and Smith ⁹⁶		CSR suggests there may be weak evidence to support

CSR, Cochrane systematic review; EMLA, eutectic mixture of local anesthetics; GC-SF, granulocyte colony-stimulating factor; NPUAP, National Pressure Ulcer Advisory Panel; RCT, randomized controlled trial.

healing of venous ulcers compared to placebo.⁹¹ The most commonly reported adverse effect of pentoxifylline treatment is gastrointestinal disturbance.⁹¹

Arterial ulcers

A nonrandomized Veterans Affairs study evaluated the success of conservative therapy in patients who had a documented ankle–brachial index <0.9 but a transcutaneous oxygen level of >30 mm Hg.⁸⁹ They found that conservative therapy, which included wound dressings and minor amputations, healed more than two-thirds of the wounds present in the study⁸⁹ and that requiring “late” revascularization did not increase the risk of mortality or amputations.⁸⁹ A Cochrane review of treatments for arterial leg ulcers found that there was insufficient evidence to validate a particular practice.⁴⁶ In our experience, topical lidocaine 1% to 2% gel applied once to twice daily can alleviate ulcer pain while patients are waiting to be revascularized.¹¹⁰

Diabetic ulcers

The standard elements of treatment for diabetic ulcers include thorough debridement, restoration of vascular perfusion, good wound care, pressure relief, and infection control.^{8,111,112} No studies have shown benefit for any particular dressing types, but MRDs are advised.^{113–115} For DFUs, there are multiple treatments approved by the FDA, including platelet-derived growth factor–based becaplermin gel (Regranex), bilayered skin constructs (Apligraf), and bioabsorbable membrane with human fibroblasts (Dermagraft).^{116–118}

Pressure reduction can be achieved with total contact casts, cast walkers, and removable shoe modifications, such as therapeutic shoes and foot pads.¹¹⁹ Total contact casts (also called nonremovable casts) are customized casts that surround the lower leg and redistribute pressure to the entire foot.¹¹⁹ Existing evidence suggests that nonremovable casts are superior to removable ones.^{93,120–122} The combination of nonremovable casts plus surgical Achilles tendon lengthening may be superior to the cast alone.¹²³ Total contact casting should be avoided in patients with severe peripheral artery disease or ongoing infection.^{111,124} Revascularization should be performed if necessary to reduce the incidence of amputation.^{94,125} Evidence suggests that aggressive surgical interventions, including surgical debridement and local limited amputation, may reduce the risk of above the ankle amputation.^{95,111,126}

Malignant ulcers

In patients with malignant ulcers, the aim is to keep the wound comfortable, clean, and free of infection.

Malignant fungating wounds are often already excessively moist and may require dressings that absorb exudate, such as an alginate. Topical metronidazole gel or charcoal-based dressings may help to control odor. Nonadherent dressings containing silicone, such as Mepilex (Mölnlycke Health Care, Gothenburg, Sweden), may also be a practical solution to prevent sticking to the wound.¹²⁷ A Cochrane review of topical agents and dressings for malignant fungating wounds found that miltefosine 6% (Miltex; Asta Medica, Frankfurt, Germany), applied as a fluid to small wounds on the breast, may slow disease.¹²⁸ This cytostatic agent has been shown to topically slow the progression of malignant breast wounds and avoid the side effects of systemic application.⁹⁶

Rheumatologic ulcers

Inflammatory ulcers caused by immune system dysregulation can rapidly become expansive non-healing wounds. These deeper wounds sometimes require dressings to control exudative excess, such as alginates or foam pads. If they are dry and necrotic, hydrogel dressings effectively improve autolytic debridement and patient comfort. Systemic treatment of rheumatologic ulcers can include the immunosuppressive ladder approach not limited to prednisone, cyclosporine, azathioprine, mycophenolate mofetil, and tumor necrosis factor inhibitors, such as infliximab.

Poor nutritional status

Inadequate protein intake impairs wound healing.⁹⁷ Patients with pressure ulcers who are fed high-protein diets showed faster healing in their ulcers compared to the lower-protein diet patients.¹²⁹ One randomized controlled trial found that among long-term care residents, protein supplementation approximately doubled the rate of ulcer healing in the treatment group compared to the control group.¹³⁰ In addition, correction of deficiencies of vitamins C, A, and zinc can lead to improved wound healing in those with restrictive diets or a history of gastric bypass surgery.¹³¹

In conclusion, dermatologists may benefit from following the TIME format for healing chronic wounds along with considering the underlying systemic diseases afflicting the patient.

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What's new: Management of venous leg ulcers

Approach to venous leg ulcers

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Learning objectives

After completing this learning activity, participants should be able to evaluate and treat the symptoms and signs of early venous disease, prevent or delay the occurrence of venous leg ulcers, assess the differential diagnosis of leg ulcers, and delineate an approach to the evaluation of leg ulcers.

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Leg ulcerations are a common problem, with an estimated prevalence of 1% to 2% in the adult population. Venous leg ulcers are primarily treated in outpatient settings and often are managed by dermatologists. Recent advances in the diagnosis and treatment of leg ulcers combined with available evidence-based data will provide an update on this topic. A systematized approach and the judicious use of expensive advanced therapeutics are critical. Specialized arterial and venous studies are most commonly noninvasive. The ankle brachial pressure index can be performed with a handheld Doppler unit at the bedside by most clinicians. The vascular laboratory results and duplex Doppler findings are used to identify segmental defects and potential operative candidates. Studies of the venous system can also predict a subset of patients who may benefit from surgery. Successful leg ulcer management requires an interdisciplinary team to make the correct diagnosis, assess the vascular supply, and identify other modifiable factors to optimize healing. The aim of this continuing medical education article is to provide an update on the management of venous leg ulcers. Part I is focused on the approach to venous ulcer diagnostic testing. (J Am Acad Dermatol 2016;74:627-40.)

Key words: leg ulcers; lipodermatosclerosis; venous disease; venous leg ulcers; wound healing.

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Abbreviations used:

ABPI:	ankle brachial pressure index
CEAP:	clinical, etiology, anatomy, and physiology
DVT:	deep venous thrombosis
LDS:	lipodermatosclerosis
TcPCO ₂ :	transcutaneous pressure of carbon dioxide
TcPO ₂ :	transcutaneous pressure of oxygen
VLU:	venous leg ulcer

INTRODUCTION

Leg ulcers are a common problem, with an estimated prevalence of 1% to 2% in the adult population, similar to the prevalence of psoriasis and alopecia areata.¹⁻³ With shifting demographics toward an aging population, sedentary lifestyles, an increased prevalence of obesity, and the emergence of various chronic diseases, leg ulcers will likely continue to be a significant burden on the health care system.^{4,5} Despite the myriad potential causes of leg ulcers, a majority are caused by vascular abnormalities, with venous disease being the most common cause. Recent advances in the diagnosis and treatment of leg ulcers combined with the latest available evidence indicate a need for an update on this topic. A systematized approach and the judicious use of advanced expensive therapeutics are critical. The aim of this continuing medical education article is to provide an update on venous leg ulcers (VLUs). Part I is focused on the diagnostic approach to VLUs. In part II, the current medical and surgical management options will be reviewed.

EPIDEMIOLOGY

Key points

- **Approximately 1.5 to 3 per 1000 adults have active leg ulcers in North America**
- **Venous leg ulcers are more common in elderly patients, but 22% of individuals develop their first venous leg ulcers by 40 years of age, and 13% by 30 years of age**

The overall incidence of venous disease has been documented to be 76.1 per 100,000 person-years.⁶ It is estimated that approximately 1.5 to 3 per 1000 North American adults have active leg ulcers.⁷ Although chronic leg ulcers may be caused by many pathologies, upwards of 70% are related to venous disease, and approximately 20% are caused by arterial insufficiency or mixed arteriovenous disease.^{8,9} The annual prevalence for individuals 65 to 95 years of age is reported as 1.69%; the overall male incidence is 0.76% and the female incidence is slightly higher (1.42%).¹⁰ Previous epidemiologic

studies identified a number of risk factors for venous disease, including the following: advanced age, female sex,^{11,12} a family history of leg ulcers, non-Hispanic white race, obesity, a history of deep venous thrombosis (DVT) or phlebitis, previous serious traumatic leg injury, chronic lower extremity edema, a sedentary lifestyle, and any occupation requiring prolonged long periods of standing.¹³⁻¹⁵

Although VLUs are more common in elderly patients, 22% of individuals develop their first VLUs by 40 years of age and 13% before 30 years of age, affecting their ability to work and participate in social activities. As a result, many patients living with chronic leg ulcers experience a diminished quality of life, acute and chronic pain, and associated physical disabilities.¹⁶ While upwards of three quarters of VLUs heal after 6 months, the annual reported recurrence rates range from 6% to 27%.^{17,18} High recurrence rates may be attributable to persistence of underlying disease and a number of psychosocial and economic factors.^{7,19} However, even when best practice pathways are implemented, only 50% to 75% of leg ulcers achieve complete healing after 6 months of treatment.²⁰

PATHOPHYSIOLOGY OF VENOUS DISEASE/VENOUS ULCERS

Pathogenesis of venous disease**Key point**

- **Valve dysfunction, outflow obstruction, arteriovenous malformation, and calf muscle pump failure contribute to the pathogenesis of venous disease**

The venous system is constructed like a ladder, with deep and superficial veins forming the 2 sides connected by perforator veins as the rungs (Fig 1). The calf muscle pump acts as a “peripheral heart,” propelling venous blood toward the heart during calf muscle pump contraction. Unidirectional valves in the vein allow blood flow in 1 direction toward the heart and prevent reverse flow or reflux. However, pooling of venous blood (venous disease) can occur if: (1) the valves are damaged from congenital conditions, trauma, recurrent infection, or inflammation caused by a DVT resulting in reverse flow or leakage around the closed valves; (2) there is obstruction associated with previous clotting with a DVT, or outflow obstruction caused by obesity, pregnancy, or a pelvic mass/growth; (3) arteriovenous malformations as a congenital disease composed of abnormal connections of arteries and veins; or (4) the calf muscle pump is ineffective because of muscle wasting, immobility, or limited

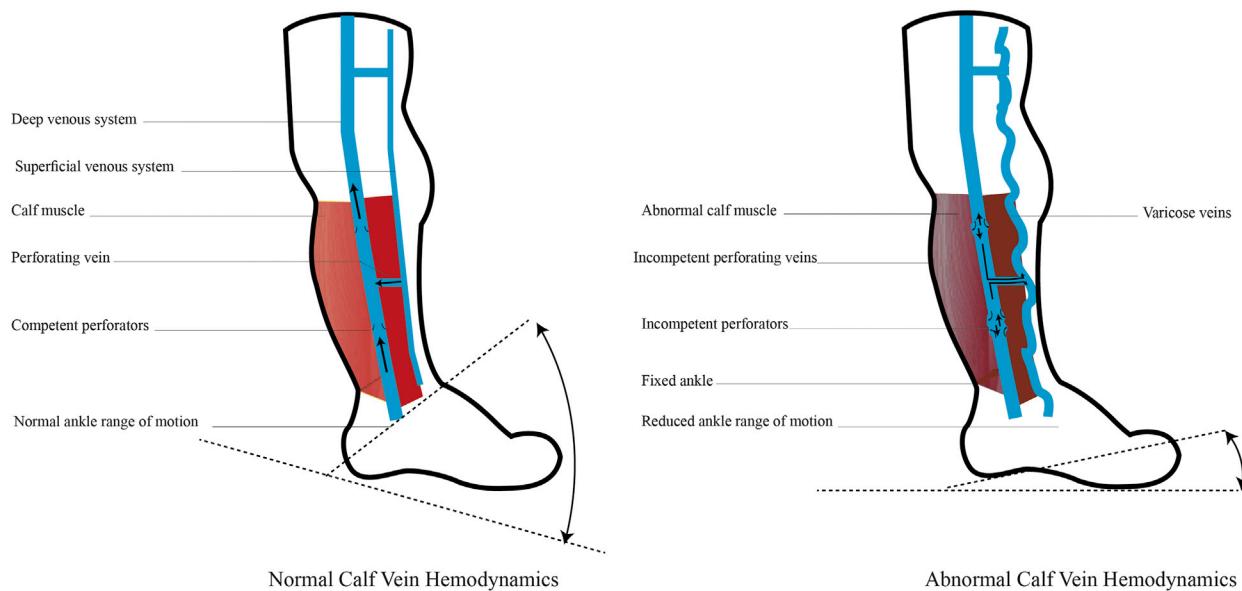


Fig 1. Venous disease. Calf vein hemodynamics.

ankle mobility (eg, neuromuscular disease, arthritis, or previous injury).

The calf muscle provides an important mechanism to propel venous blood flow toward the heart. During calf muscle pump contraction, the deep veins empty and blood flows from the superficial to the deep veins through the perforating veins. Venous pressure therefore drops during ambulation.²¹⁻²³ Venous reflux or obstruction—either superficial or deep—is linked to venous disease and the clinical manifestations of chronic insufficiency. An elevated venous pressure creates a retrograde buildup of pressure into the venules of the skin, leading to sustained increased ambulatory venous pressures (also called venous hypertension) that has been associated with development of leg ulceration.²³

None of these theories fully explain the underlying pathophysiology that leads to venous leg ulceration, including fibrin cuff theory, inflammatory trapping, and altered cytokine, growth factor, and matrix metalloproteinase profiles.²⁴ None of these theories fully explain the observed pathophysiology.

In 1982, Burnand et al^{25,26} postulated that an elevated intravascular pressure stretches the vascular wall and dilates the endothelial pores, allowing extravasation of red blood cells into the dermal tissue, promoting hemosiderin deposition and hyperpigmentation of the skin. Fibrinogen leaks into the interstitium and polymerizes to become fibrin that gathers around the capillary walls in bands called “fibrin cuffs.”^{25,26}

It has been speculated that these fibrin cuffs cause skin changes by compromising oxygen diffusion and entrapping various growth factors (ie, the growth

factor trap hypothesis).²⁷ In addition, venous hypertension leads to margination and activation of various inflammatory cells (ie, the white cell trap hypothesis). Histologic studies indicate that venous disease is associated with the accumulation and adhesion of macrophages and T-lymphocytes in the perivascular and dermal matrix. A number of phospholipids, including phosphatidylcholine, a chemokine for macrophages responsible for a cascade of inflammatory responses, can be found attached to incompetent valves. High levels of interleukin (IL)-1 alfa, IL-1 beta, and tumor necrosis factor-alpha can be found in the wound fluid of difficult to heal VLUs. Other abnormalities associated with chronic recalcitrant VLUs include the upregulation of protease activity, especially matrix metalloproteinase, abnormalities of erythrocyte innate immunity, and factor XIII-mediated inhibition of fibrinolysis.^{28,29}

Pathogenesis of nonhealing wounds

Key point

- The relationship between inflammation and protein expression in venous leg ulcers is not clear

Genetic expression of beta catenin, c-myc, and properdin are elevated in keratinocytes of nonhealing VLUs. However, the relationship between inflammation and genetic expression in VLUs is not clear.^{30,31} Transforming growth factor beta (TGF- β) receptors are downregulated in tissue samples from patients with chronic VLUs.³² The attenuation of TGF- β signaling leads to activation of the small body

size against decapentaplegic signaling cascade and a subsequent loss of tissue hemostasis with associated hyperproliferation.³² These findings express an abnormal gene signature often related to the refractory wounds along with the role of cytokines and inflammasomes or large proteins, which are potent inducers of ILs-1 β and -18 during inflammation.³³

Cost

Key points

- **Chronic wounds in general are responsible for \$7 billion per year in annual health care costs worldwide, with venous leg ulcers being the most common type of leg ulcers**
- **The average cost for a venous leg ulcer is estimated as \$16,000 per treatment episode in the North American population**
- **The prevalence of venous leg ulcers in the elderly is as high as 1% to 2% of the elderly population in North America**

As the population ages, the prevalence and economic burden of VLUs is increasing.^{10,34,35} The annual health care system cost of VLU management in the United States has been estimated at \$1.5 to \$3.5 billion.^{17,36}

Based on this analysis, the average cost for VLU therapy is estimated at \$16,000 per treatment episode.³⁶ The total annual cost of the treatment of VLUs has been reported as \$25 million in Scandinavia and \$200 million in England.^{1,37}

In a recent study, patients with VLUs consumed more medical resources compared to non-VLU patients, with more days missed from work and a 29% higher cost from lost work.³⁸ Chronic wounds in general are responsible for \$7 billion per year in annual health care costs worldwide, with VLUs being the most common cause of leg ulcers.^{10,39} The major costs have moved from inpatient costs to outpatient care and nondrug treatments; nursing visit times and bandaging systems are the most expensive components.

Spectrum of disease

Key point

- **Patients with venous disease have a spectrum of skin presentations from edema, hemosiderin staining, venous eczema, venous starburst of veins radiating distally from the medial malleolus (ie, corona phlebectatica paraplanaris), lipodermatosclerosis, and atrophie blanche along with ulcer formation**

Chronic venous disease refers to a spectrum of changes ranging from varicose veins and hyperpigmentation to stasis dermatitis to lipodermatosclerosis



Fig 2. Corona phlebectatica paraplanaris or blood vessel burst extending distally from medial ankle.

(LDS) and VLUs.²⁴ VLUs commonly present as shallow ulcers in the gaiter area—the area extending from midcalf to approximately 1 inch below the malleolus.^{10,28} Patients with venous disease have a spectrum of skin presentations ranging from edema (pitting or nonpitting), hemosiderin staining, venous eczema, venous starburst of veins radiating distally from the medial malleolus (ie, corona phlebectatica paraplanaris [Fig 2]), LDS, and atrophie blanche along with ulcer formation.⁴⁰

In order to standardize the reporting and comparing of the diverse manifestations of chronic venous disorders, a comprehensive classification system (clinical, etiology, anatomy, and physiology [CEAP]) has been developed. An international committee of the 1994 American Venous Forum introduced a simplified classification for chronic venous disorders. CEAP is clinically used for those in vascular medicine but has not yet been validated or linked to clinical outcome.

The fundamentals of the CEAP classification include a description of the clinical class (C) based upon objective signs, the etiology (E), the anatomic (A) distribution of reflux and obstruction in the superficial, deep, and perforating veins, and the underlying pathophysiology (P), whether caused by reflux or obstruction.⁴¹ Although CEAP classification has not been validated or been shown to correlate with outcome, it does provide a framework to classify disease (Table I).

LDS, or inflammation of the skin and fatty tissue causing woody changes in the dermis (C4), is part of this spectrum and presents as indurated plaques of the lower extremities (Fig 3). Acute phase LDS is exquisitely painful and is commonly misdiagnosed as cellulitis, phlebitis, inflammatory morphea, or other panniculitides. The chronic phase of LDS presents with induration and fibrosis that usually

Table I. Clinical, etiology, anatomy, and physiology classification of chronic venous disease

Clinical classification	Etiologic classification	Anatomic classification	Pathophysiology
C0: No visible or palpable signs of venous disease	Ec: Congenital	As: Superficial veins	Pr: Reflux
C1: Telangiectases or reticular veins	Ep: Primary	Ap: Perforating veins	Po: Obstruction
C2: Varicose veins	Es: Secondary	Ad: Deep veins	Pr,o: Reflux and obstruction
C3: Edema	En: No venous cause identified	An: No venous location identified	Pn: No venous pathophysiology identified
C4a: Pigmentation or eczema			
C4b: Lipodermatosclerosis or atrophy blanche			
C5: Healed venous ulcer			
C6: Active venous ulcer			
S: Symptomatic, including ache, pain, tightness, skin irritation, heaviness, and muscle cramps, and other complaints attributable to venous dysfunction.			
A: Asymptomatic.			



Fig 3. Lipodermatosclerosis. Note the inflammation of the skin presenting as indurated fibrosing plaques of the lower extremities.

precedes any associated ulceration.²⁸ If LDS is left untreated, complications may arise and the woody fibrosis may extend distally to the feet and toes, eventually resulting in venolymphedema (and association of venous disease and lymphedema).

VLU commonly present as shallow ulcers in the area extending from the midcalf to approximately 1 inch below the malleolus (ie, the gaiter area; Fig 4).¹⁰ The border is often serpiginous, with an irregular shape, and the wound base generally has a preponderance of pink granulation and yellow fibrinous tissue. Most patients have edema and discomfort or aching that is worse at the end of the day and may be exacerbated by dependency.

Differential diagnoses of venous disease/ venous leg ulcers

Key points

- Approximately 10% of lower extremity wounds are atypical with less common etiologies



Fig 4. Venous leg ulcers. Note the shallow ulcer with a yellow fibrinous base that is commonly found on the medial aspect of the ankle.

- **Histology is often essential for the diagnosis of an atypical wound**

Although the majority of chronic wounds are caused by vascular, neuropathic, and pressure etiologies, the early diagnosis of atypical wounds is critical. An estimated 10% of lower extremity wounds are caused by less common etiologies, including infections, skin cancers, metabolic disorders, inflammatory processes, and other diagnoses. Fig 5 lists the differential diagnoses for painful ulcers.

Histology is often essential for the diagnosis of an atypical wound. In a retrospective study of 350 biopsy specimens obtained from chronic wounds, 29.7% were identified as atypical, with malignancy detected in 24 patients (17%).⁹ In a study on 144 patients with VLUs, Senet et al⁴² obtained at least two 6-mm punch biopsy specimens, 1 at the wound edge and 1 in the wound bed, in the most clinically suspicious areas. In this study, the overall frequency of skin cancer in patients with chronic leg ulcers was reported to be as high as 10.4%.⁴²

Picture	Painful ulcers	Location	Characteristics	Common associations	Diagnostics	Management
	Pyoderma gangrenosum	any	inflamed, undermined elevated edges, sterile pustules	inflammatory bowel disease, hematoproliferative disorders, rheumatoid arthritis, antineutrophilic cytoplasmic antibody positive vasculitis	history and clinical characteristics	topical steroid ^{39,21} topical tacrolimus ^{39,21} oral corticosteroids ^{39,40} cyclosporine ^{39,40,21} anti TNF alpha ²¹ mycophenolate Mofetil ^{39,40}
	Vasculitis	dependent areas	palpable purpura, atrophia blanche, livedo reticularis, pustules	autoimmune disorders, cryoglobulinemia, infections	biopsy, urinalysis, medical work-up	oral corticosteroids ^{41,43} cyclosporine ⁴¹ dapsone ⁴¹ colchicine ⁴¹⁻⁴³ methotrexate ⁴² azathioprine ⁴²
	Martorell ulcer	posterior lateral overlying achilles tendon	livedo reticularis necrosis	hypertension, diabetes, vitamin K antagonists	biopsy	surgery ^{8,11} skin graft ^{8,11} control of blood pressure ¹¹ prostaglandin E ¹³⁵ platelet-derived growth factor ¹² hyperbaric oxygen ⁴⁴
	Calciphylaxis	any	livedo reticularis necrosis	chronic renal failure, hyperparathyroidism, kidney transplant recipients, warfarin	biopsy, history	control of hyperparathyroidism or parathyroidectomy ⁴⁵ Sodium thiosulfate ⁴⁵⁻⁴⁷ warfarin/enoxaparin ⁴⁵⁻⁴⁷ hyperbaric oxygen ⁴⁵⁻⁴⁷ tissue plasminogen activator ⁴⁸
	Sickle cell ulcer	medial ankle	very painful polycyclic wound, absence of vital granulation tissue	sickle cell anemia	history, sickle cell prep	blood transfusion ^{49,60} hydroxyurea ^{49-51,52} arginine butyrate ⁵³ nitric oxide ⁵³ Hypomethylating agents ⁵³ compression therapy local wound care
	Arterial leg ulcer	around lateral malleolus, pretibial area, dorsum of foot and toes	punched out skin defect, often with eschar and/or necrotic border	coronary arterial disease, intermittent claudication, rest pain	ankle-brachial-index(ABI), duplex, angiography	Revascularization ²⁸ Medical therapy ²⁸ local wound care pain management
	Hydroxyurea ulcer	medial and lateral ankle	painful progressive skin defect with white ulcer base and absence of vital granulation tissue	history of essential thrombocythosis, polycythemia, vera, myeloproliferative disorder	history of medication use	cessation of hydroxyurea ^{54,4} skin substitutes ⁵⁴ compression therapy local wound care pain management
	Anti-phospholipid syndrome	any	necrotic ulcer livedo reticularis	livedo racemosa, purpura, ecchymosis, acrocyanosis, raynaud's, venous thromboembolism, arterial thrombosis, fetal loss	IgG/IgM anticardiolipin antibody, lupus anticoagulant, VDRL, beta2-glycoprotein 1	Anticoagulants ⁵⁵ systemic corticosteroids ⁵⁶ intravenous immunoglobulins ⁵⁷

Fig 5. Differential diagnosis of painful leg ulcers. (The authors acknowledge Professor Jurge Hafner's help in making the table.)

As the population ages, the rate of peripheral arterial disease is increasing. Based on several studies, a venous etiology was identified in >50% to 75% of leg ulcers, with mixed arteriovenous ulcers accounting for ≤15% of the remaining patients.^{23,43}

APPROACH TO VENOUS LEG ULCERS

Key points

- A comprehensive history and physical examination are essential in the evaluation of chronic venous insufficiency and ulceration

- Varicose veins in the medial thigh and calf may implicate involvement of the great saphenous vein; dilated veins in the antero-lateral thigh and knee are related to anterior saphenous insufficiency

A comprehensive history and physical examination are required for an accurate diagnosis (Fig 6). Information should include symptoms, exacerbating and alleviating factors, medical history (particularly of previous DVTs), and other clotting disorders. Coagulation disorders are a significant but often

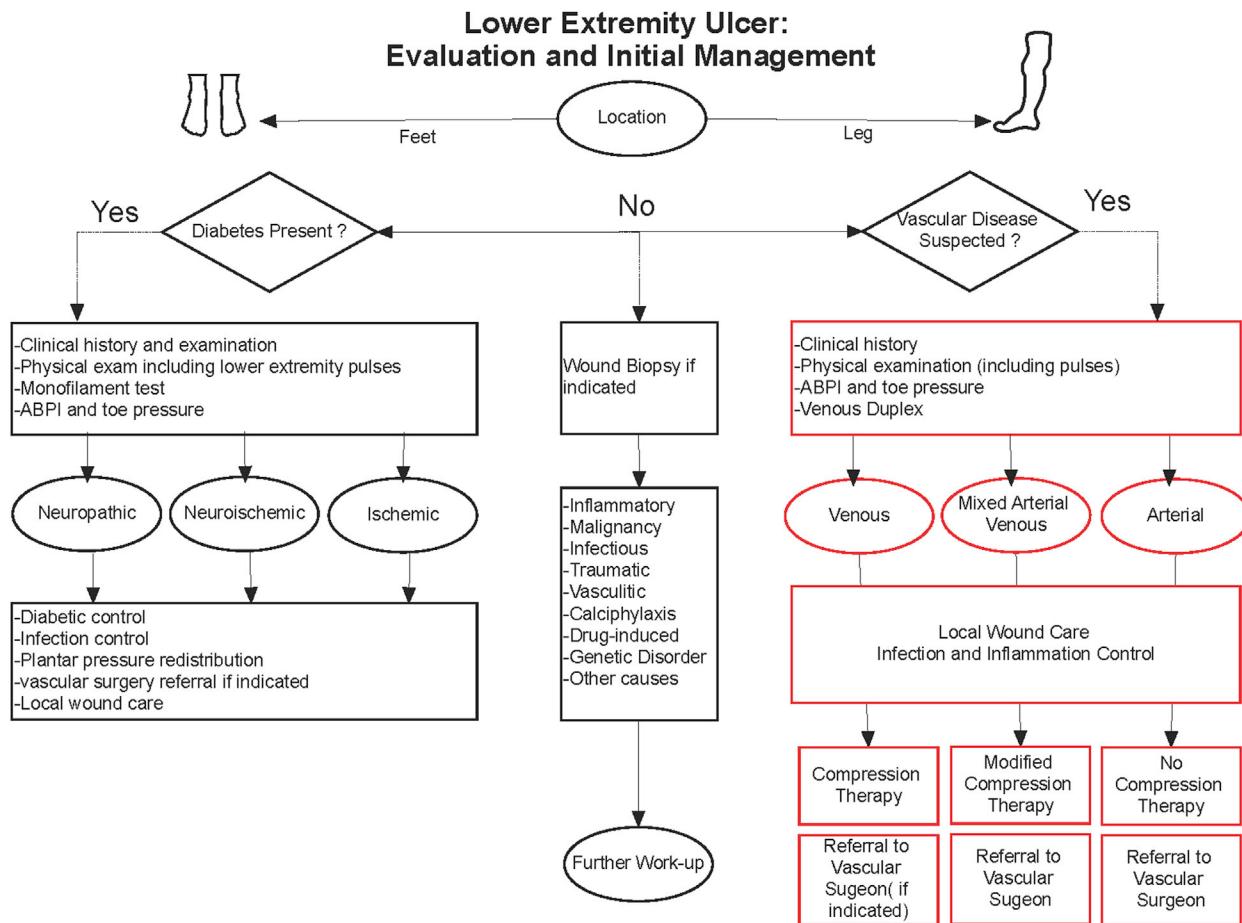


Fig 6. Evaluation and initial management of a lower extremity ulcer.

unrecognized risk factor for venous disease, especially in younger patients.^{44,45} Factors that affect the calf muscle pump, such as arthritis, should be documented. Typical complaints of VLUs include: aching and heaviness, often at the end of the day, fatigue, restless legs, night cramping, and itching often associated with venous eczema and swelling. Symptoms can be exacerbated by prolonged standing or sitting, and difficult to control edema may be affected by the menstrual cycle. It is important to carefully assess patients with VLUs to be sure that the symptoms are in fact originating from chronic venous disease and not coexisting conditions, such as cardiac failure. A physical examination focusing on skin changes, limb size and shape, and vascular assessment is critical. The pattern of varicosities provides a clue to the possible location of venous disease. Varicose veins in the medial thigh and calf may implicate involvement of the great saphenous vein; dilated veins in the anterolateral thigh and knee are related to anterior saphenous insufficiency.⁴⁶ Other clinical findings may include edema, hemosiderin pigmentation, LDS, and venous eczema.

The arterial system should be assessed in all patients, including palpation of pulses, assessment of foot temperature, and measurement of the ankle brachial pressure index. Patients should also undergo testing for peripheral neuropathy and ankle range of motion.

Margolis et al⁴⁷ found an association of VLUs with other comorbidities, and it is therefore important for physicians to consider a proper assessment for associated diseases, including anemia, diabetes mellitus, and depression.⁴⁷

Assessment of factors that delay healing

Key points

- Failure of venous leg ulcer healing has been correlated with a larger initial area of the wound, longer duration of the wound, history of venous ligation or vein stripping, history of hip or knee replacement surgery, an ankle brachial pressure index <0.8, and >50% of the wound being covered by fibrin
- Large wound size, nonadherence to compression therapy, the involvement of

all 3 venous valvular systems (ie, superficial, perforating, and deep venous), older age, being overweight (a body mass index $\geq 25 \text{ kg/m}^2$), and history of deep venous thrombosis are associated with nonhealing and venous leg ulcer recurrence

It is important to assess risk factors for the development of leg ulcers and factors that delay the healing of VLUs. VLUs at the highest risk for nonhealing could potentially benefit from the advanced therapies to treat stalled but healable venous ulcers. Failure of VLU healing has been correlated with a larger initial area of the wound, longer duration of the wound, a history of venous ligation or vein stripping, a history of hip or knee replacement surgery, an ankle brachial pressure index <0.8 , and $>50\%$ of the wound covered by fibrin (firm yellow base).^{1,34} Franks et al⁴⁸ studied 411 patients with nonhealing VLUs and determined associations with larger wound size, longer wound duration, poor lower limb joint mobility, and general immobility.⁴⁸ The rate of recurrence for VLUs has been reported to be as high as 37% at 3 years and 48% at 5 years.⁴⁹

In an unselected group of 157 VLUs studied by Labropoulos et al,⁴⁹ 80% of the ulcers healed (131/157) with a proper diagnosis, appropriate surgical intervention, adequate compression therapy, and optimal local wound care. Triple venous system disease or involvement of superficial, perforating, and deep veins was the greatest risk factor associated with nonhealing. These findings suggest a potential role of venous valvular surgery to correct incompetence.^{18,49}

In summary, a number of factors have been identified to be associated with nonhealing and recurrent VLUs: larger wound size, nonadherence to compression therapy, triple venous valvular system disease, older age, overweight patients with a high body mass index ($>25 \text{ kg/m}^2$), and a history of DVT.⁴⁹ A history of DVT was detected in 60% of patients with VLUs; however, more patients may have an undiagnosed DVT. Patients with nonhealing ulcers (refractory to 6 months of treatment) had a 5-fold greater chance of having a history of DVT.⁴⁹ Patients with VLUs are commonly overweight and also have a relative nutritional deficiency that needs to be addressed.³ Environmental factors, especially cold temperatures, may also play an important role in the onset of chronic leg ulcers.²³ VLU prevalence shows a reduction in VLUs in summer and a rise in VLUs in winter. In addition, there was a statistically significant negative correlation between higher temperatures and new ulcer onset.²³

Wound assessment

Key points

- Accurate and consistent wound measurement is important to monitor the healing rate
- If a wound is not 30% smaller by week 4 it is unlikely to heal by week 12, and the patient should be reassessed for the appropriate diagnosis and management

The documentation of the wound location, wound area, and characteristics is important for the monitoring of healing and treatment effectiveness. Wound assessment requires an accurate measurement that is precise, user-friendly, and reproducible.⁵⁰

Traditional wound area measurements include measuring length and width in perpendicular distances of wound borders (ie, the longest length with the greatest width at right angles), manual tracing, and digital photography. These methods are inconsistent and sometimes inaccurate. Wound tracings that calculate the area via digital software are slightly better than linear measurement.^{51,52} The wound surface is measured by a tracing of the wound surface on a sterile disposable contact layer and then calculating the wound area to provide more accurate and reproducible wound measurement. Software programs can also calculate wound dimensions from a photograph of the lesion.⁵³ This method avoids any contact with the surface of the wound, reducing potential pain and bacterial contamination of the wound surface.

Many observational studies support the correlation between improvements of the geometric parameters of the wound margin, a healthy wound bed, and progression to wound healing.⁵⁴ Cardinal et al⁵⁴ reported that wounds with symmetrical convex geometries (ie, oval or circular wounds) at baseline heal better than wounds with large concavities, multiple segments, and skin islands at the margins. In summary, wound documentation is important for documenting healing rates. If a wound is not 30% smaller by week 4 it is unlikely to heal by week 12, and the patient should be reassessed for the appropriate diagnosis and management.⁵⁵ Stalled but healable chronic wounds are ideal candidates for advanced therapies.

Wound biopsy

Key points

- The proper site from which to obtain the biopsy specimen depends on the etiology of the wound and appropriate selection of the biopsy site

Table II. Common stains and markers used in wound pathology*

Stains and markers	Function
Hematoxylin–eosin	Regular
Periodic acid–Schiff	Vessel walls and basement membrane, fungi
Phosphotungstic acid-hematoxylin	Stains muscle fibers and fibrin, especially fibrin thrombi
Verhoff–van Gieson	Stains elastin to differentiate a venule from an arteriole
von Kossa stain	Identify the calcium deposits.
Fite	Leprosy/acid-fast bacilli
Zeihl–Neelsen	Tuberculosis/acid-fast bacilli
Giemsa	Leishmaniasis
Perl potassium frocyanate	Hemosiderin
CD31	Endothelial marker for vascular lesions
D2-40	Detects podoplanin in lymphatic endothelial cell
Factor VIII	a marker for mast cells and platelet thrombi

*Data from Labropoulos et al⁴⁹ and Cardinal et al.⁵⁴

- Multiple biopsy specimens are occasionally required for difficult diagnostic situations, and especially for the detection of localized malignancy**

Obtaining a biopsy specimen of a wound is an easy and helpful diagnostic procedure to identify less common etiologies if a wound has unusual presentation, is in an unusual location, if malignancy is suspected (such as nonhealing wounds in burn scars), and in wounds that fail to heal after standard care.^{9,56}

Wound biopsy specimens provide valuable diagnostic histologic findings, including the diagnosis of malignancy, infection, and other causes.⁵⁶ In some cases, evaluation may include tissue culture or obtaining an additional biopsy specimen for immunofluorescence to detect immune complexes (ie, vasculitis, connective tissue disease, or inflammatory skin disorders) using specialized transport media.⁵⁶ The proper site from which to obtain the biopsy specimen depends on the etiology of the wound and appropriate selection of the biopsy site. Multiple biopsy specimens are occasionally required for difficult diagnostic situations, especially for the detection of localized malignancy. The preferred techniques for obtaining wound biopsy specimens are punch or elliptical biopsy specimens taken from the edge of the ulcer to compare the ulcerated area and surrounding skin.⁵⁰ Hematoxylin–eosin is the most widely used stain in wound pathology, but the selection of special stains depends on the differential diagnosis (Table II).^{50,57}

The biopsy specimen—usually taken from the center of the wound—should be sent for culture to rule out viral, bacterial, fungal, and atypical infections. Atypical mycobacterial and deep fungal infections characteristically occur in immunosuppressed individuals or because of direct inoculation.

Special staining can be used to identify the organism and direct appropriate and selective antimicrobial therapy.⁹

There is a reluctance to obtain a biopsy specimen from a patient with LDS because of the risk of nonhealing.^{40,58} The biopsy specimen is commonly consistent with sclerosing panniculitis, and the most dramatic changes occur in the subcutaneous fat. However, the clinical picture of LDS is protean, and the limited biopsy specimens obtained show a variety of changes based on the stage of the disease. The presence of other pathologies, such as pyoderma gangrenosum or vasculitis, as the basis of venous disease is not unlikely.

VASCULAR ASSESSMENT: ARTERIAL AND VENOUS

After a comprehensive clinical assessment, subsequent noninvasive and sometimes invasive investigations may be indicated to confirm the diagnosis and plan treatment options. Assessment of the arterial system to rule out mixed arteriovenous disease is important. Up to 25% of patients with a VLU have concomitant peripheral arterial disease.^{59,60}

Investigation of the arterial system

Investigation of the arterial system includes a review of both micro- and macrocirculation. Microcirculation assessment includes transcutaneous oxygen saturation ($TcPO_2$), laser Doppler flowmetry, and transcutaneous carbon dioxide saturation ($TcPCO_2$) measurements and capillaroscopy. Macrocirculation assessment includes the ankle brachial pressure index (ABPI) and toe pressure, Doppler arterial waveforms, duplex ultrasonography, angiography, and magnetic resonance imaging.

Table III. Arterial measurements related to vascular supply of the leg*

ABPI	Toe pressure	Toe brachial index	Ankle Doppler wave form	Diagnosis
>0.8	>80 mm Hg	>0.6	Normal/triphasic	No relevant arterial disease
>0.5	>50 mm Hg	>0.4	Biphasic	Some arterial disease: modify compression
>0.4	>30 mm Hg	>0.2	Biphasic/monophasic	Arterial disease predominates
<0.4	<30 mm Hg	<0.2	Monophasic	High risk for limb ischemia

ABPI, Ankle brachial pressure index.

*Data from Sibbald et al.⁶⁸

Microcirculation/transcutaneous oxygen

Key points

- Transcutaneous oxygen saturation, laser Doppler flowmetry, and transcutaneous carbon dioxide saturation are sensitive indicators of microcirculation
- The transcutaneous oxygen saturation measurement reflects oxygen supply to the end organ (the skin) by the combination of the macro- and microcirculation

Different techniques can evaluate microcirculation in patients with wounds. TcPO₂, laser Doppler flowmetry, and TcPCO₂ measurements and capillaroscopy have been used clinically.⁶¹ Transcutaneous oximetry measures tissue oxygenation in superficial skin layers by placing an electrode on the skin surface. TcPO₂ is correlated with arterial oxygen pressure in neonatal skin, but the variation in adult skin thickness interferes with this linear relationship.^{61,62} However, this method should not be used in isolation. The values are influenced by edema, skin temperature, and infection.⁶² TcPO₂ is an important value, especially because it reflects the net oxygen supply to the end organ (the skin) by macro- and microcirculation.

Macrocirculation

ABPI and toe brachial pressure index. ABPI is a noninvasive screening tool that offers 85% sensitivity and 97% specificity to detect arterial occlusive disease.⁶³ The ankle systolic blood pressure alone reflects the amount of blood flow to the ankle that is influenced by central blood pressure. The ankle pressure is divided by the best estimate of the central pressure (the higher of the 2 brachial blood pressures), which results in the ABPI (ie, ABPI is equal to the ankle Doppler pressure [for each leg] divided by the highest brachial Doppler pressure).

Normal ABPI measurements range from 0.9 to 1.3.^{64,65} In general, indices <0.8 signify some arterial disease and may be associated with intermittent claudication; indices <0.5 indicate severe ischemia. The upper cutoff point of 1.3 has been generally

accepted. Allison et al⁶⁶ identified a strong association of cardiovascular disease with ABPI >1.4, which is most commonly seen in those with noncompressible calcified vessels.

The ABPI Doppler measures macrovascular arterial disease and may overestimate the true pressure reading in patients with arterial calcification and advanced atherosclerosis caused by diabetes mellitus.^{64,67,68} About 80% of patients with diabetes and 20% of nondiabetic patients have calcified, noncompressible arterial vessels.⁶⁷ In these cases, ankle vessels are not compressible with a cuff—such that any ABPI >1.3 may be related to spuriously elevated ankle pressures. These individuals have unreliable ABPI measurements, and a direct toe systolic pressure (or toe brachial pressure index) is more reliable because the digital arteries are rarely heavily calcified (Table III). The current standard for detection of significant peripheral arterial disease is an ABPI <0.8 or a toe pressure <55 mm Hg.⁶⁸

Doppler arterial waveforms. Doppler arterial waveforms can be attained at the same time as assessment of the ankle systolic pressure with the Doppler probe. A normal waveform is triphasic and becomes biphasic if mild disease exists proximal to the probe insonation placement site and monophasic in the presence of more severe disease.

The Doppler pulse wave is influenced by arterial distensibility and arterial stiffness. The pulse waves can be either detected by audible Doppler or documented by pulse wave velocity. A higher pulse wave velocity correlates with the stiffer arterial wall. The relationship between ABPI and wave velocity has been studied.⁶⁹

Duplex ultrasonography. Duplex ultrasonography is a noninvasive, accurate test for the evaluation of the flow in the arteries and veins. It provides accurate noninvasive information relating to cross-sectional areas and provides the ability to view vessel walls in a longitudinal plane from several angles.

Duplex ultrasonography detects changes in the velocity of red cells. Duplex ultrasonography imagers are now available as relatively

inexpensive lightweight, portable machines. This high level of sensitivity may allow the noninvasive duplex technique to replace angiography as the criterion standard in these patients.³⁴ Experienced vascular technologists working in an accredited vascular laboratory provide expert vascular images for meaningful interpretation. Partnership with a high-quality vascular laboratory is important to obtain useful arterial and venous measurements.

Angiography. Angiography remains the criterion standard for arterial assessment because of its ability to successfully outline the entire arterial system. It has an advantage over various noninvasive technologies for patients who are obese, individuals with extensive vessel calcification, and in the presence of bilateral diffuse atherosclerotic disease or arteriovenous malformations. The assessment of pressures across a stenotic vascular lesion provides accurate hemodynamic information of the pressure gradient created by the lesion and, therefore, the severity of the arterial stenosis. One of the primary criticisms of angiography is the production of anatomic images to represent a functional deficit. Intra- and interoperator interpretation are also variable. Direct mortality rates caused by cardiac arrest or stroke are low; however, significant morbidity can arise from bleeding from the arterial puncture site, cholesterol and thrombus embolization to the legs, arterial wall dissection, contrast dye allergy, renal failure from the dye related hemoconcentration, and arteriovenous fistula formation. These complications prohibit the frequent use of angiography either for diagnostic or follow-up purposes. Therefore, angiography is now primarily reserved for preoperative evaluation, interventional procedures, thrombolysis, and emergency situations where other modalities are not available.

Magnetic resonance imaging. A magnetic resonance imaging scan using gadolinium to enhance the contrast is a diagnostic tool that can detect small and large vessels and the ability of the perfused tissue to extract oxygen. Increasingly detailed anatomic information may be obtained using computed tomography of magnetic resonance angiography. Between duplex ultrasonography and computed tomography or magnetic resonance angiography, the diagnosis of the severity of arterial disease and its location can be determined. Percutaneous angiography is only performed to define a target vessel for surgical bypass.

Investigation of the venous system

Investigation of the venous system can be conducted using venous Doppler ultrasonography,

color flow duplex ultrasonography, air plethysmography, or venography.

Venous Doppler ultrasonography. Venous Doppler ultrasonography with the use of a handheld Doppler unit for assessment of the venous system is not recommended because of the higher sensitivity and specificity of duplex ultrasonography.

Color flow duplex ultrasonography. This highly operator-dependent, noninvasive test provides both anatomic and flow data, allowing for detailed and accurate assessments of reflux and patency within individual veins. The accuracy of duplex ultrasonography for defining venous reflux in the deep, superficial, and perforator veins is important. With duplex ultrasonography, the operator can first identify the vein in question with the ultrasound function, and then investigate the specific vein for reflux or obstruction—this is not possible with handheld duplex ultrasonography.

This test has the capacity to distinguish thrombus age, clot mobility at the tip of the clot, and the length of the free-floating tail of the clot. Venous thrombus can be detected in the large vessels down to the level of the popliteal vein, and good visualization of the deep and superficial calf veins is possible. Recent studies reported that duplex scanning is the best test to monitor thrombi and to check reflux after DVT. The exact localization of reflux within the superficial and deep systems can also be determined using this technique. This procedure is different than the procedure used to evaluate DVT. However, it is important to remember that an anatomic diagnosis of venous disease by duplex ultrasonography does not always correspond to a clinical diagnosis.¹³

Air plethysmography. This simple, noninvasive test quantitatively assesses venous reflux, obstruction, and poor calf muscle pump function. A polyurethane tubular air chamber surrounds the entire leg and is connected to a computer. Readings are taken throughout the procedure, and small changes in limb volume reflecting an increased venous blood volume are detected electronically through the use of an air-filled chamber or sleeve surrounding the limb. Plethysmography is able to identify abnormal venous function by rapid refilling of the venous tree, resulting in leg swelling with limb dependence that can be caused by either abnormal reflux or obstruction. This test is almost always abnormal in cases of venous ulceration.⁷⁰

Venography. Venography is an invasive test that has been replaced by color flow duplex ultrasonography for most clinical indications. This technique provides additional information on thrombus age, valve damage, and a much wider view of the venous system for reconstructive surgery. In cases of venous

obstruction, it provides a road map for stenting procedures to reopen obstructed venous segments. The risks include severe contrast media allergy, associated cardiac arrest, or acute renal failure.

In conclusion, venous ulcers are the most common leg ulcers and must be distinguished from other vascular ulcers, including mixed arteriovenous and arterial ulcers. The differential diagnosis of leg ulcers includes a wide range of entities that must be identified. When wounds are not healing at the expected rate in spite of treatment, skin biopsy specimens should be obtained and bacterial cultures might be helpful diagnostic tools. Specialized arteriovenous studies are most commonly noninvasive. The ABPI can be performed with a handheld Doppler unit at bedside, and duplex Doppler ultrasonography performed by the vascular laboratory can identify segmental defects and potential surgical candidates. Vascular laboratory studies of the venous system can also predict which patients will benefit from surgery. Successful leg ulcer management requires an interprofessional team to make a specific diagnosis and to assess the vascular supply and other modifiable factors for optimal healing.

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What's new: Management of venous leg ulcers

Treating venous leg ulcers

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Learning objectives

After completing this learning activity, participants should be able to identify appropriate therapeutic strategies linked to venous and other leg ulcer diagnoses based on the evidence, highlight the role of compression therapy as the key component of venous leg ulcer management, assess educational methods to improve patient adherence to compression and other health promotion measures posthealing, and evaluate venous ulcer patients for referral to specialized centers and when to use adjunctive therapy.

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Venous leg ulcers account for approximately 70% of all leg ulcers and affect 2.2 million Americans annually. After a comprehensive patient and wound assessment, compression therapy remains the cornerstone of standard care. Adjuvant care with topical or systemic agents is used for wounds that do not heal within 4 weeks. Once healed, long-term compression therapy with stockings or surgical intervention will reduce the incidence of recurrence. This continuing medical education article aims to outline optimal management for patients with venous leg ulcers, highlighting the role of a multidisciplinary team in delivering high quality care. (J Am Acad Dermatol 2016;74:643-64.)

Key words: management; medical therapy; surgical intervention; varicose veins; venous leg ulcers.

INTRODUCTION

Venous leg ulcers (VLUs) are an important medical problem. The chronic and recurrent nature of VLUs causes morbidity, severely reduces quality of life, and increases the cost of health care. Standard

evidence-based care includes compression therapy and the use of adjunctive agents, which have been shown to accelerate healing, improve quality of life, and likely reduce cost.¹ Emerging therapies, including venous surgical interventions, hold

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Abbreviations used:

ABPI:	ankle brachial pressure index
BSE:	bilayered skin equivalent
CVI:	chronic venous insufficiency
EST:	electrostimulation therapy
FDA:	US Food and Drug Administration
IPC:	intermittent pneumatic compression
LDS:	lipodermatosclerosis
MPFF:	micronized purified flavonoid fraction
MTS:	May-Thurner syndrome
NPWT:	negative pressure wound therapy
RCT:	randomized controlled trials
SEPS:	subfascial endoscopic perforator surgery
VLU:	venous leg ulcer

promise, particularly in the prevention of ulcer recurrence. Before initiating treatment, a comprehensive patient and wound assessment should be performed to evaluate coexisting conditions that may impair healing. This includes addressing anemia, hypoproteinemia, malnutrition, thrombophilia, and patient behaviors, such as smoking (Fig 1).¹⁻⁴ In an effort to better understand the basis of treatment, a brief review of underlying pathophysiology is warranted. In healthy patients in the upright position, the venous system must overcome the force of gravity to facilitate the return of blood to the heart. The 2 main forces that make this return possible are active calf muscle contraction (augmented by ankle movement) and the reactive closing of the venous valves. These 2 forces work in concert to propel venous return and prevent retrograde blood flow.² A defect in any component of these 2 pathways can lead to venous insufficiency. These defects can include outflow problems, such as venous obstruction, or calf muscle impairment caused by deep venous thrombosis and reflux problems related to dilated veins or incompetent venous valves. In a compromised venous system, venous pressure is not reduced but rather sustained (as opposed to being reduced, which normally occurs) during leg exercise, such as walking, and this is referred to as sustained ambulatory venous pressure or venous hypertension. Sustained ambulatory venous pressure increases hydrostatic pressure within the venous system. The increased hydrostatic pressure forces fluid containing proinflammatory molecules to leak into interstitial tissue. This triggers a cascade of physiologic changes and edema formation, leading to ulcer formation (detailed in part I of this continuing medical education article).

COMPRESSION THERAPY

Key points

- **Compression therapy is critical for the care of venous leg ulcers because it corrects impaired venous return**



Fig 1. Common clinical pictures of venous leg ulcers, which present as shallow ulcers over the medial malleolus surrounded by pigmentary changes.

- **Compression therapy is the mainstay of treatment for patients with venous leg ulcers and can be provided by 3 different techniques: (1) bandage systems, (2) stockings/hosiery, or (3) intermittent compression devices**

The physiologic effects of compression include accelerating venous flow, reducing venous reflux and edema, promoting oxygenation in the surrounding dermal skin tissue, and eventually stimulating fibrinolysis.³

Compression therapy can be provided through 3 techniques or types of compression systems. The first is sustained wear bandage systems, typically comprised of ≥ 2 components. The second is through removable stockings or hosiery. The third is through intermittent compression devices, which are pumps used periodically throughout the day. These compression techniques or systems have several different methods to deliver external pressure to the venous system.

Compression bandages

Compression bandages are classified as either elastic (long stretch) or inelastic (short stretch). Elastic bandages have an extensibility of 100% to 200%; inelastic bandages have an extensibility of 40% to 99%. Elastic bandages contain elastomeric fibers that provide easy stretchability and a sustained “squeeze” as the bandages recoil to their original length (Fig 2, A). Optimal use of elastic bandages occurs when the bandage is stretched from the relaxed state to the stopping distance (ie, maximum stretch), then relaxed and applied at 50% stretch to exert elastic energy in both directions of the bandage (Fig 2, B). By contrast, inelastic bandages are rigid and resist lateral expansion of the calf muscle during active contractions, such as when walking.

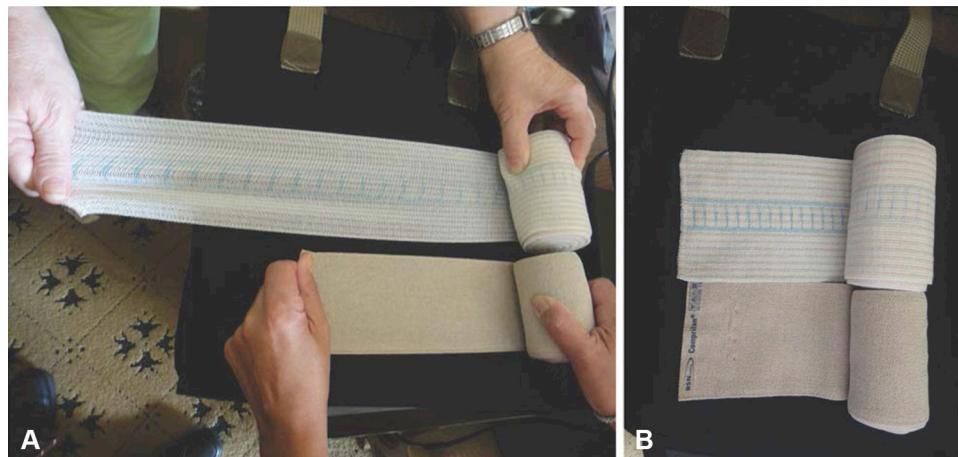


Fig 2. Compression bandages. **A**, Elastic or long stretch bandages with extensibility of 100% to 200%. **B**, Inelastic or short stretch bandages with extensibility of 40% to 90%.

With walking, calf muscle contraction is supported externally by the rigid bandage, thereby improving venous return. Inelastic bandages therefore provide compression during activity and also when fluids pool (ie, edema formation) with standing; however, they do not compress the limb at rest in a supine position. An Unna boot is a classic example of an inelastic bandage.

Compression bandages may be comprised of a single component or multiple components. Multicomponent bandages often have an initial protective layer of orthopedic wool padding, and may also include a crepe retention layer, an elastic compression bandage, and an outer elastic cohesive bandage to prevent slippage. When used correctly, both elastic (long stretch) and inelastic (short stretch) bandages are effective. A recent metaanalysis found both types of bandages to be equally efficacious in promoting healing of VLUs in both ambulatory and nonambulatory patients.⁴ Nonetheless, inelastic bandages may have added benefit in some clinical situations through exertion of lower resting pressure compared to the higher resting pressure of elastic systems. As a result, inelastic bandages may be less likely to exacerbate pain or restrict arterial flow in patients with coexisting arterial disease. However, inelastic bandages can be challenging to use because of bandage slippage and a more rapid decrease of compression pressure over time. Table I shows examples of different available compression bandaging systems.

Subbandage pressure increases with the addition of each layer, supporting the notion that multiple layers are superior to single-layer compression. The principles of compression are based on the modified Laplace law⁸:

$$\text{Subbandage pressure} =$$

$$\frac{\text{No. of layers} \times \text{tension} \times \text{constant}}{\text{Bandage width} \times \text{limb circumference}}$$

Subbandage pressure can be increased with additional bandage layers, increased tension of the applied bandages, and decreased bandage width or limb circumference.⁹

Compression bandages can be applied using a number of techniques. A common practice is the application of bandages in a spiral fashion around the leg with a 50% overlap between turns, producing a double layer of wrapping with each component. Other application techniques, such as the figure 8 bandage technique, increase the number of effective overlapping layers, thereby increasing compression. Therefore, while a bandage may have 4 components, it may actually have many more layers. Any effective compression is dependent on accurate application of bandages by knowledgeable and skilled personnel.^{5,10,11}

Healing is influenced by patient and wound characteristics. Wound size and duration are the 2 most common characteristics affecting healing. Marston et al¹² reported that 57% of VLUs seen in clinical practice treated with compression healed in 10 weeks and 75% healed in 16 weeks. Larger ulcers ($>20 \text{ cm}^2$) and mixed arteriovenous ulcers were associated with delayed healing. Other risk factors for poor healing include long-standing VLUs, often associated with lipodermatosclerosis, and previous knee or hip surgery.

A recent analysis of 36 studies and 2 Cochrane systematic reviews found that overall there is no difference in ulcer healing, time to ulcer healing, or ulcer recurrence between compression stockings

Table I. Types of compression bandage systems⁵⁻⁷

Compression system	Examples	Advantages	Disadvantages
Long stretch (elastic) bandages	Surepress, Ace, Dauerbinde, and Biflex Thusane	<ul style="list-style-type: none"> • Base of the toes to knees • Low working pressure • High resting pressure • >140% extensibility • Can be applied spiral or figure of 8 • Inexpensive, washable, and reusable forms available 	<ul style="list-style-type: none"> • Tend to unravel • Do not provide sustained compression • Risk of incorrect application
Short stretch (inelastic) bandages	Zinc paste (viscopaste/Unna), Comprilan, Circaid (Velcro), FarrowWrap (Velcro), Action, Panelast, and Porelast	<ul style="list-style-type: none"> • Comfortable/better tolerance • Minimal interference with daily activities • Generate high working pressure • Certain bandages with Velcro 	<ul style="list-style-type: none"> • Gauze impregnated with different products, such as zinc oxide • Not good for highly exudative wounds • Need to be applied by well trained staff
Intermittent compression devices	Pneumatic pump	<ul style="list-style-type: none"> • Enhance fibrinolytic activities 	<ul style="list-style-type: none"> • Expensive • Require immobility for a few hours a day
Multicomponent bandages	Coban 2 (and Coban2 lite), Profore, and Actico and Sofban	<ul style="list-style-type: none"> • Higher compression • Graduated compression • Sustain a high compression • Lite compression available for patients with mixed venous arterial disease 	<ul style="list-style-type: none"> • Need to be applied by well trained staff
Compression devices	Variable	<ul style="list-style-type: none"> • Adjustable compression • Easy to put on and remove • Easy to use 	<ul style="list-style-type: none"> • Expensive
Support system	Tubigrib	<ul style="list-style-type: none"> • Double layer to increase compression 	<ul style="list-style-type: none"> • Bulky • Low compression

Trade names remain property of their respective manufacturers.

and compression bandages. Compression stockings are most often used as a maintenance therapy after VLUs have healed (Fig 3). However, stockings represent a treatment option for some patients. An example of their potential healing benefit was shown in a recent study by Ashby et al¹⁰: 457 patients with VLUs were randomized into 2 groups; 1 group was treated with 2 layered stockings and the other was treated with 4-layer bandages. A high dropout rate was recorded in the stocking group because of discomfort and pain (38% in hosiery group vs 28% in the group with bandages), and healing rates of VLUs did not differ between therapies.¹⁰ The authors suggested that the use of stockings might result in higher quality adjusted life-years because patients who often preferred stockings and had an overall lower cost than those with bandages.¹⁰ In theory, the use of compression stockings during treatment also prepares patients for lifelong use of stockings as maintenance compression therapy.¹³ Table II shows the recommended level of compression stockings in patients with venous disease.^{16,17}



Fig 3. Compression stockings.

Intermittent pneumatic compression devices

Intermittent pneumatic compression (IPC) devices deliver sequential pressure to the limb and can be used in combination with bandages or stockings. Particularly in nonambulatory patients, IPC can be a beneficial adjunct to other forms of compression.^{2,18} An air pump and inflatable auxiliary boots in a closed system are used to provide

Table II. Compression stockings

Class	Pressure at ankle (mm Hg)	Indications
I	20-30	Mild edema, varicose veins, and venous ulcers
I	30-40	Moderate edema, moderate venous disease, varicose veins, and venous ulcers
III	40-50	Severe edema, severe venous disease, venous ulcers, and lymphedema
IV	50-60	Lymphedema

Adapted from Mosti¹⁴ and Woo et al.¹⁵

dynamic compression, thereby stimulating calf muscle contraction.¹⁹ IPC prevents lower limb edema and skin changes that are frequently seen on the legs of immobile patients.

Indications and contraindications for compression therapy

Key points

- High compression of 40 mm Hg should be considered for a person with an adequate vascular supply indicated by an ankle brachial pressure index of 0.8 to 1.2
- In patients with mixed arteriovenous ulceration (with an ankle brachial pressure index >0.5 and an absolute ankle pressure of >60 mm Hg), inelastic compression <40 mm Hg does not impede arterial perfusion and treats impaired venous return

Arterial supply may be evaluated by performing an ankle brachial pressure index (ABPI),²⁰ a screening tool with high sensitivity (85%) and specificity (97%) for the detection of arterial occlusive disease.²¹ The ABPI is calculated by the ankle systolic pressure divided by the best estimate of the central pressure (ie, the higher of each arm's brachial systolic blood pressure). Limbs with an ABPI >0.8 should have sufficient arterial supply to safely tolerate application of high strength compression therapy (Table III). An ABPI >1.2 usually indicates severe calcification or glycosylation of the tibial arteries leading to falsely elevated ankle pressure readings.

In patients with venous disease and coexisting arterial compromise (ABPI 0.5-0.8) compression therapy may need to be modified.²³ Recent studies have shown that inelastic compression may be superior to elastic compression in enhancing arterial circulation and healing.^{14,24,25} In patients with an ABPI >0.5 and an absolute ankle pressure of >60 mm Hg, Mosti et al²⁵ reported that inelastic

Table III. Compression therapy level based on ankle brachial pressure index²²

ABPI	Compression therapy
0.8-1.2	High compression therapy
0.5-0.8	Modified compression therapy (≤ 20 mm Hg)
<0.5	No compression therapy

ABPI, Ankle brachial pressure index.

Data from Briggs et al.²²

compression <40 mm Hg does not impede arterial perfusion and may lead to a normalization of venous function. While careful observation is warranted, inelastic bandages are recommended in the management for patients with mixed arteriovenous leg ulcers.²⁵ Alternatively, bandage systems with fewer components may also be applied, thereby modifying the compression force. However, inappropriately high compression can be harmful because it can lead to arterial compromise and subsequent distal gangrene and limb loss in individuals with severe arterial or arterial predominant disease.^{14,24,25} For this reason, compression in a patient with any degree of arterial insufficiency should be performed carefully and with a discussion of the risk of complications.

Patients with congestive heart failure may have difficulty tolerating compression therapy. Lower limb compression may increase the preload volume and worsen congestive failure.³ To prevent sudden exacerbation of heart failure, it is suggested to first apply modified compression therapy on 1 leg. If congestive failure is not exacerbated after 48 hours of observation, then increasing compression to both legs can be attempted.

Areas of inappropriate high pressure present as irregular pressure marks and deep or nonuniform erythema of the skin after removal of compression wraps. These areas may require the insertion of padding or other protective materials. Pain can alert patients and clinicians to problems associated with inappropriate compression therapy, which can indicate arterial compromise.

PAIN MANAGEMENT

Key points

- Pain is subjective: “Pain is whatever the experiencing person says it is”
- Appropriate treatment is determined by the severity and specific types of pain: nociceptive, neuropathic, or a combination

VLUs greatly affect quality of life, in large part because of pain. Table IV lists different pain etiologies in patients with VLUs. Appropriate

Table IV. Different pain etiologies in patients with venous leg ulcers

Pain in patients with venous leg ulcers
Ulcer-related
Neuropathy and nerve damage
Lower leg edema
Lipodermatosclerosis
Superficial and deep vein phlebitis
Infection
Contact dermatitis
Atrophie blanche

treatment of pain is determined by the severity and specific type of pain: nociceptive, neuropathic, or a combination.¹⁵ Stress induced by pain causes cortisol release and elevated cytokine levels, potentially delaying wound healing.²⁶ Pharmacotherapy continues to be the mainstay of treatment.

A patient-oriented multifaceted approach is recommended for the management of wound-related pain to provide relief and restore overall activities of daily living. The World Health Organization's analgesic ladder states that mild pain (1-3 on a 10-point scale) can be treated with acetaminophen, aspirin, or nonsteroidal antiinflammatory drugs (NSAIDs). However, these agents should be used with caution in people >65 years of age.¹⁵ Because of the risk of renal failure and worsening of congestive heart failure, narcotics are reserved for moderate (4-7 out of 10) or severe pain (8-10 out of 10), with initial use of short-acting and weak agents, followed by long-acting and stronger agents.¹⁵

Recent studies indicate that nociceptive and neuropathic pain may coexist in patients with VLUs.²⁷ Nociceptive pain is stimulus-dependent, incurred by tissue damage activating pain receptors in the skin, muscle, bone, joints, and ligaments, and is often described as tender, aching, throbbing, or gnawing. Neuropathic pain is spontaneous, not stimulus-dependent, and often described as burning, stinging, shooting, or stabbing. Neuropathic pain can initially be treated with the off-label use of tricyclic antidepressant medications. VLU size, duration, location, or severity of underlying venous disease does not predict the severity of the associated pain.²² The Krasner model²⁸ divides pain into 3 components: continuous chronic pain associated with underlying venous disease, acute recurrent pain with dressing change, and acute incidental pain associated with procedures, such as debridement or a secondary infection. Patients with early stages of venous disease, especially with prominent varicosities, often describe a dull aching or heaviness in their legs at the end of the day. Additional

aggravating factors include lower leg edema from prolonged periods of standing and pelvic venous disease, often associated with obesity.

Pain can peak during dressing changes with cleansing or debridement. Careful selection of dressings withatraumatic adhesives (eg, silicone and nonadherent wound contact layers) has been shown to limit skin damage and minimize pain during dressing changes.^{29,30}

Sealants, barriers, and protectants, such as wipes, sprays, gels, and liquid roll-ons, are designed to protect the periwound skin from caustic wound exudate and trauma induced by adhesive dressing removal. Pain from debridement can be alleviated by topical anesthetics or systemic pain medication 30 minutes before the procedure.³¹

Wound cleansing can also be painful, especially with the application of cold cleaning solutions. In addition to cytotoxicity, strong antiseptics may cause stinging and pain. Physical manipulation using forceps and gauze across wound beds can cause tissue damage. To reduce trauma during cleansing, compresses or soaks can be applied at room temperature and may be preferred to the physical trauma associated with wound irrigation.

Complications of venous disease

Lipodermatosclerosis (LDS) is the main clinical finding associated with long-standing venous disease. Although there is uncertainty regarding the exact pathogenesis of LDS, the most dramatic changes in histopathology include thickening and fibrosis of the septae with lipophagocytic changes and adipocyte necrosis (sclerosing panniculitis).³²

Chronic LDS commonly presents with hyperpigmentation and induration. Nearly half of patients with LDS experience pain, even in the absence of an ulcer. Acute LDS is characterized by intense pain and may occur even in the absence of other signs of venous disease. Management of acute LDS includes the use of intralesional corticosteroids, NSAIDs, fibrinolytic agents, and compression if tolerated. Stanozolol, oxandrolone, or danazol may be useful for patients who do not respond to other therapeutic options.³²

Superficial or deep phlebitis must also be considered when patients describe new localized pain or a change in preexisting pain. Superficial phlebitis presents as bruise-like pain over a localized portion of an inflamed vein. The pain is often aggravated by palpation or standing, and the involved area may be warm to the touch. Deep phlebitis of the lower leg is often associated with more intense, often excruciating pain and swelling that must be distinguished



Fig 4. Debridement. Removal of biofilms and necrotic tissue with curettage.

from other conditions, including cellulitis or a ruptured Baker cyst.

Chronic venous insufficiency (CVI) promotes extravasation of inflammatory cells, rendering affected individuals prone to dermatitis. Dressings, bandages, and compression hosiery can cause local irritation and may aggravate the dermatitis. Allergic contact dermatitis to topical medications must be suspected in patients with dermatitis. Venous stasis dermatitis may be differentiated from allergic contact dermatitis by patch testing.

Regardless of the cause, patients with dermatitis may present with localized itching, pain, or increasing wound size despite wound treatment (Fig 4). Allergic contact dermatitis to wound and skin care products delays healing (Fig 5).^{33,34} Allergic contact dermatitis is more prevalent in individuals with VLUs than individuals with any other dermatologic condition. Up to 80% of patients with VLUs have ≥ 1 positive patch test reactions, with most of the identified allergens relating to previous allergen exposure or a history of contact dermatitis.³³ This typically results from long-term exposure to allergens under occlusion and the impaired barrier function of the ulcerated skin.³³

Common allergens in perfumes and derivatives include colophony, Balsam of Peru, and perfume mix. Other common contact allergens associated with leg ulcers include preservatives, such as formaldehyde, quaternium 15 (a formaldehyde releaser), and propylene glycol. Hydroxybenzoate or other preservatives found in creams and some paste bandages are also potentially allergenic.³⁵ Preservative-free zinc bandages are an attractive alternative. Hydrogel is a common irritant/allergen because of the preservatives, including propylene glycol. In a study of 39 patients with chronic wounds, the rate of sensitization to hydrogel ranged from 9% to 23%.^{36,37} The most common allergens found in wound products are listed in Table V.^{20,36,38-51}



Fig 5. Allergic contact dermatitis to wound-related products.

Another cutaneous manifestation of venous disease is atrophie blanche,⁵² consisting of distinct white, stellate depressed atrophic scars frequently associated with local severe and sharp pain. Although the exact mechanism is unclear, in patients without associated venous disease it is often caused by small vessel thrombosis (livedoid vasculopathy).⁵²

LOCAL WOUND CARE

Debridement

Key point

- **Debridement is integral to wound care by removing devitalized tissue, foreign material, abnormal/dysfunctional cells, bacteria, and their byproducts, including biofilms**

Although routine debridement for VLUs is not yet supported by randomized clinical trials, the best available evidence suggests that debris on the wound surface should be removed.^{53,54}

Using a large retrospective dataset, Wilcox et al⁵⁴ documented faster healing with weekly debridement ($P < .001$) of a variety of chronic wounds compared to every 2 weeks. Wound debris can include devitalized tissue, foreign material, abnormal/dysfunctional cells (ie, nonresponsive or senescent cellular burden), and bacteria often associated with biofilms and bacteria byproducts (Fig 4). Necrotic tissue is rarely found in VLUs not complicated by arterial disease or infection. However, if present, debridement of necrotic tissue in chronic wounds can be achieved using a number of methods: surgical removal of slough or sharp debridement to bleeding tissue; autolytic dressings, including calcium alginates, hydrogels, hydrocolloids, or biologics (eg, maggots); and enzymatic methods (eg, collagenase [Table VI]).⁵⁵

Methods of debridement may be deployed as a single therapeutic modality or may be combined to optimize the debridement process. Selecting the proper combination of debridement techniques requires evaluation of the patient's individual needs while taking into account the available clinical resources.⁵⁴ Awareness of debridement options and the value of maintenance debridement

Table V. Contact dermatitis to wound products in patients with VLUs

Allergen	Evidence	Dressing category	Product examples
PG	Freise et al ³⁸ (2008), Trookman et al ³⁹ (2011), and Renner et al ³⁶ (2013)	Hydrogel or emulsion	Hydrogels contain PG: • Intrasite gel: Has PG as backbone • Solugel: Benzoyl peroxide, PG • Saf-gel: Sodium alginate, PG • Biafine topical emulsion Honey dressings
Propolis	Pasolini et al ⁴⁰ (2004) and Garrido Fernandez et al ⁴¹ (2004)	Foam or gel	
Pentaerythroid ester of hydrogenated rosin	Pereira et al ⁴³ (2007) and Renner et al ³⁶ (2013)	Hydrocolloid	NuDerm and DuoDerm
Sorbitan sesquioleate	de Waard-van der Spek et al ⁴³ (2007)	Nonadhesive dressings	Adaptic
Lanolin/paraben	Trookman et al ³⁹ (2011)	Cream or compress	Biafine topical emulsion and Seltouch
Colophony	Pereira TM et al ⁴²	Cream	Biafine topical emulsion
Carba mix	Isaksson et al ⁴⁴ (2004)	Rubber in elastic bandages	Tensor bandages
Povidone—iodine	Lachapelle ⁴⁵ (2005), Saap et al ⁴⁶ (2004), and Velazquez et al ⁴⁷ (2009)	Solution, paste, or PEG gauze	PVP-I and cadexomer iodine
Chlorhexidine digluconate	Shoji ⁴⁸ (1983)	Gauze, foam, or nonadhesive dressings	AMD and Bactigras
Silver	Renner et al ³⁶ (2013) and Ozkaya ⁴⁹ (2009)	Hydrofiber	Aquacel Ag
Benzalkonium chloride	Dao Jr et al ⁵⁰ (2012)	Creams/cleansers	Revitaderm wound care gel
Neosporin	Gehrig and Warshaw ⁵¹ (2008)	Cream/ointment	Neosporin
Bacitracin	Gehrig and Warshaw ⁵¹ (2008)	Cream/ointment	Baciqueut and polysporin

Trade names remain property of their respective manufacturers.

AMD, Antimicrobial foam dressing; PEG, percutaneous endoscopic gasterostomy; PG, propylene glycol; PVP-I, polyvinylpyrrolidone of iodine.

procedures is a practice gap in contemporary dermatology.⁵⁶ High-quality studies are needed to elucidate the role of debridement in VLU care.⁵⁷

Dressings

Key points

- A moist wound environment is essential to all phases of wound healing
- Moisture retentive dressings include foams, alginates, hydrofibers, hydrogels, and hydrocolloids

A moist wound environment is essential to all phases of wound healing. It accelerates the reepithelialization process and collagen synthesis. It also facilitates the action of growth factors, keratinocyte and fibroblast proliferation, and promotes angiogenesis.

Venous ulcers are typically heavily exudative, and the exudate contains inflammatory proteases and cytokines capable of attacking surrounding healthy

skin if the exudate is not removed efficiently from the wound surface. In VLUs, the management consideration typically is not how to maintain a moist wound environment but how to avoid a macerated, overly wet wound environment in the presence of toxic mediators. The frequency of dressing changes should be chosen based on the absorptive capacity of the dressing applied. Once a dressing becomes saturated, it should be replaced.

Many dressings have been developed to maintain moisture balance. The major categories of moisture-retentive dressings include foams, alginates, hydrofibers, hydrogels, and hydrocolloids^{58,59} (Table VII). However, newer dressings require less frequent dressing changes and may be more cost effective with reduced nursing time.⁶² Dressing selection is based on the wound characteristics, control of exudate, odor, and protection of peri-wound skin.⁶³

Table VI. Debridement methods³⁹

Methods	Advantage	Disadvantage	Contraindication
Surgical/sharp	Fast; high selectivity	Painful; requires skilled person; expensive	Ischemic tissue and bleeding disorders
Autolytic	Less pain; inexpensive	Monitor infection closely; may promote anaerobic growth	Infected wounds and friable skin
Mechanical	Inexpensive	Nonselective; time-consuming; painful	Clean wounds
Biological: Maggot/ Larva	Inexpensive; selective; safe; simple procedure	Short lifespan; time-consuming; not meant to be used under compression	Bleeding diathesis; deep, tunneled wounds; allergy; adhesives, eggs, fly larvae, and soy beans
Enzymatic	Nonselective; less painful; fast	Expensive; requires skilled person; may require secondary specific dressing; not meant to be used weekly	Allergy: the enzyme preparation

Infection control

Key points

- Because of increasing bacterial resistance, antimicrobial drugs should be reserved only for cases of clinical infection or when bacteria are thought to be present in sufficient number to inhibit the healing process
- Topical antimicrobial dressings may contain silver, iodine, honey, polyhexamethylene biguanide, or a combination of methylene blue and crystal violet

When bacterial growth reaches a critical threshold of $>10^5$ bacteria per gram of tissue, bacterial toxins can cause tissue damage in the superficial wound compartment and delay healing.⁵⁵ Soft tissue infection (deep and surrounding tissue) requires systemic antibiotics. No evidence currently supports the routine use of systemic antibiotics for VLUs.⁶⁴

Bacteria are thought to inhibit healing without inducing a host response as seen in cellulitis. These dressings are effective if the active antimicrobial barrier agent comes into direct physical contact with free-flowing (planktonic) bacteria. With the increasing problem of bacterial resistance, antimicrobial preparations should be reserved only for cases of clinical infection or antiseptic agents that have multiple antibacterial actions, lessening the chance of resistance. For example, ionized silver exerts its active antimicrobial barrier activity against cell walls, cytoplasmic membranes, and the DNA structure of microorganisms. The healing benefits of silver antimicrobial barrier dressings remain controversial.⁶⁵

Medical therapy

Key points

- Pentoxifylline has several mechanisms of action, such as increasing the deformability

of erythrocytes, the inhibition of neutrophil adhesion/activation, and the inhibition of tumor necrosis factor-alfa

- Flavonoids and anticoagulants may have a role in the management of venous leg ulcers

Pentoxifylline. Pentoxifylline improves VLU healing, especially in ulcers that have been present for >1 year. In an early systematic review performed by Jull et al,⁶⁶ pentoxifylline was found to improve VLU healing by approximately 50%.⁶⁷

Pentoxifylline is a methylxanthine derivative with good oral absorption and an extensive first-pass metabolism in the liver before excretion in the urine.⁶⁸ Peak plasma level is reached within 2 hours, with a half-life of 4 to 6 hours. The usual dose is 400 mg 3 times daily, with lower doses recommended in patients with significant renal failure. However, some investigators have reported higher doses of pentoxifylline (800 mg 3 times daily) to be more effective than the standard doses.^{69,70} Maximum benefits may be observed after 2 to 4 months of therapy.

Pentoxifylline has several mechanisms of action, including increasing the deformability of erythrocytes and inhibition of neutrophil adhesion and activation. It is also a known inhibitor of tumor necrosis factor-alfa, which has been hypothesized to impair healing of VLUs.⁷¹

Common side effects include nausea, gastrointestinal discomfort, dizziness, headache, and prolonged bleeding time.⁷⁰ Pentoxifylline has 2 primary contraindications: intolerance to methylxanthine derivatives and severe cardiac disease. The US Food and Drug Administration (FDA) pregnancy category for pentoxifylline is C.^{6,72,73}

Flavonoids. The FDA has not yet approved Daflon 500, a micronized purified flavonoid fraction

Table VII. Main categories of dressings. Adapted from Ficarelli et al⁶⁰ and Park et al⁶¹

Class	Description	Advantage	Disadvantage
Films	Semipermeable adhesive sheets	<ul style="list-style-type: none"> • Translucent • Impermeable to fluid and bacteria • Permeable to gas and water vapor • Less dressing change, less pain 	<ul style="list-style-type: none"> • Adherent, nonabsorbent • Not good for fragile skin • Risk of allergic contact dermatitis to adhesives
Hydrogels	Polymers with high water content	<ul style="list-style-type: none"> • Donates moisture • Nonpainful and soothing 	<ul style="list-style-type: none"> • Amorphous form needs secondary dressing • Caution in infected wounds • Risk of allergic contact dermatitis to propylene glycol or other components
Hydrocolloids	Hydrophilic colloid particles bound to polyurethane film, some composed of gelatin, pectin, and carboxy methylcellulose	<ul style="list-style-type: none"> • Autolytic debridement • Self-adhering • Long wear time • Impermeable to fluids and bacteria • Conforms to wound shape 	<ul style="list-style-type: none"> • Nonabsorptive • Trauma with removal • Allergy to adhesives • Risk of maceration of surrounding skin • Malodor • Needs secondary dressing
Calcium alginates	Seaweed-based complex polysaccharide; sheets wick laterally and ropes wick upward	<ul style="list-style-type: none"> • Hemostatic • Autolytic debridement • Semipermeable • Highly absorptive • Highly absorptive • Nontraumatic in removal • Highly absorbent • Conforms to wound shape • Permeable to water and vapor 	
Hydrofibers	Sheets or ribbons		<ul style="list-style-type: none"> • Needs secondary dressing
Foams	Polyurethane foam fluid exchange with partial fluid retention if variable pore size		<ul style="list-style-type: none"> • Bulky and may macerate surrounding skin, particularly with uniform pore size • Opaque • Bulky • Opaque
Composites	Multilayered combination to increase absorbency, fluid lock, and autolysis	<ul style="list-style-type: none"> • Absorbent and may be with an island and border configuration for central absorbency and peripheral adhesion 	
Collagen-based dressings	Bovine-derived collagen dressings	<ul style="list-style-type: none"> • Promote healing with oxidized reduced cellulose • Decrease matrix metalloproteinases 	<ul style="list-style-type: none"> • Not indicated for infected wounds

(MPFF), or other flavonoids for the treatment of VLUs, but these medications are available elsewhere. Flavonoids are a diverse group of naturally occurring phlebotropic compounds that are commonly used as food supplements. Daflon is a micronized flavonoid fraction used in the treatment of CVI. It improves venous tone, supports lymphatic drainage, and protects microcirculation.^{74,75} Daflon 500 mg twice daily for 6 months decreases the inflammatory response and the clinical symptoms of CVI.⁷⁴ Horse chestnut seed extract, derived from *Aesculus hippocastanum*, contains flavonoids. In several randomized controlled trials (RCTs), it was found to be safe and effective in the management of edema associated with venous disease.^{75,76}

A Cochrane review examined the role of flavonoids in the management of VLUs and found 9 studies with 1075 participants. MPFF (Daflon 500), consisting of micronized desomin and flavonoids, improved the healing rate in the treatment of VLUs through inhibition of the inflammatory cascade.^{77,78} However, the review concluded that the quality of the trials were poor and the observed increase in healing rate must be interpreted with caution.⁷⁹

Anticoagulants

Key points

- **Laboratory evaluation for thrombophilia may be considered in patients with a history of recurrent venous thrombosis and in**

young patients with chronic recurrent venous leg ulcers

- **A history of deep venous thrombosis may be detected in up to 60% of patients with venous leg ulcers**

A recent clinical trial reported that the use of low molecular weight heparin (LMWH) accelerated wound healing.⁸⁰ A RCT of 284 patients with VLUs treated with compression therapy, surgical intervention, and daily subcutaneous injection of LMWH for 12 months was found to accelerate wound healing.⁸¹ However; routine use of LMWH for VLUs, particularly if the patient does not have other reasons to be on anticoagulation.⁸²

Sulodexide is an oral antithrombotic and fibrinolytic agent with an active mixture of glycosaminoglycan polysaccharides. Sulodexide is used in the treatment of a number of vascular disorders associated with an increased risk of thrombosis, including VLU.⁸⁰ Sulodexide has a longer half-life than heparin but has less effect on systemic clotting and bleeding. In addition, sulodexide exerts antiinflammatory, endothelial-protective, and pleiotropic vascular effects, supporting its potential efficacy as an adjunct to compression therapy in patients with VLUs.⁸³

Doxycycline

Doxycycline has antiinflammatory actions, is antiapoptotic and antiantigenic, and has inhibitory effects on tumor necrosis factor-alfa and matrix metalloproteinases.⁸⁴⁻⁸⁶ Doxycycline 100 mg twice daily, in combination with compression therapy, may improve the healing of recalcitrant ulcers.^{84,87} A subantimicrobial dose (40 mg daily), has also been used with success in the treatment of patients with VLUs in a small case series, but RCTs are lacking.⁸⁶

Zinc

A 2012 Cochrane review on the role of zinc sulfate in the treatment of patients with VLUs reported no beneficial effect.⁸⁸ Six small trials ($N = 183$) were included. Four trials considered only patients with VLUs and compared oral zinc sulphate with placebo; there was no statistically significant difference between the 2 groups (relative risk, 1.22 [95% confidence interval, 0.88-1.68]).⁸⁸

SURGICAL AND PERCUTANEOUS INTERVENTIONS

Key points

- **Invasive surgeries are being replaced by less invasive percutaneous procedures, such as radiofrequency therapy, endovascular laser**

ablation, and ultrasound-guided foam sclerotherapy

- **Recalcitrant venous leg ulcers may be associated with compression of the iliac venous system or vena cava (May-Thurner syndrome)**

Several studies suggest a role of venous intervention in the care of patients with VLUs. The compression therapy alone versus compression plus surgery in chronic venous ulceration (ESCHAR) trial compared compression alone to compression plus surgery for patients with VLUs. While both groups of patients had similar healing at 6 months, surgery reduced the recurrence of healed VLUs compared to compression alone. Overall, both groups had 65% healing at 24 weeks, but 12-month ulcer recurrence were significantly reduced in the compression and surgery group (12% vs 28%).⁸⁹ After 4 years, the recurrence rate was 56% in the compression group compared with 31% for the combined compression plus surgery group ($P < .01$).⁸⁹

Percutaneous procedures, such as endovenous ablation (EVA) and ultrasound-guided foam sclerotherapy, are replacing invasive surgery.⁹⁰ EVA either by laser or radiofrequency is minimally invasive and has a short recovery time. Rare complications include deep venous thrombosis (0.3-7% of cases), which typically resolves with short-term anticoagulation.⁹¹ In comparison to surgical procedures, EVA procedures have equivalent safety and efficacy to surgical ligation/stripping of saphenous veins.⁹¹ In addition to patients with ulcers, symptomatic patients with edema, varicose veins, and skin changes are candidates for endovenous ablation.^{92,93}

Understanding the venous anatomy is important for those performing vascular intervention; anatomic differences in disease may cause different clinical manifestations and require specific intervention(s). For example, great saphenous vein reflux is typically associated with varicosities of medial thigh and calf with medial ankle ulcers. Involvement of the small saphenous vein with reflux is associated with posterior calf and popliteal fossa varicosities and lateral ankle ulceration.⁹² Therefore, in patients who might be candidates for venous intervention, comprehensive assessments with venous duplex ultrasonography are required before intervention.^{93,94} One study found that 30% of patients with VLUs had a normal deep venous system, with their venous insufficiency related to saphenous or perforator dysfunction.¹² In patients with deep vein involvement, the ligation of the femoral or popliteal veins as a routine treatment is not recommended.⁸²

Table VIII. A review of literature on use of artificial skin substitutes in the management of venous leg ulcers (2004-2014)^{82,93,99-125,162}

Name	Description	Advantage	Disadvantage	Study	Study outcome
Epidermal					
Autologous					
EpiDex	Cultured from outer root sheath keratinocytes derived from plucked anagen hair follicles, (pluripotent stem cells for hair follicles)	Cost effective	<ul style="list-style-type: none"> • Easily damaged/torn during early wound healing • 30-min air drying required after application • Long preparation time (≤ 28 days) 	Ortega-Zilic et al ¹¹⁸ (2010) O'Donnell Jr and Lau ¹¹⁹ (2006)	No RCT available Systematic review
Allogenic					
HP802-247	Allogenic tissue made of growth-arrested, human keratinocytes and fibroblasts delivered in a fibrin matrix	Long shelf life (6 months)	Must be applied weekly	Goedkoop et al ¹²⁶ (2009) Kirsner et al ¹²⁷ (2012)	Patients were given 1 of 6 different doses of HP802-247 administered once per week over 12 weeks; mean complete closure was 40% for HP802-247 vs 33% for placebo patients 205 patients were assigned in a 1:1:1:1:1 ratio to 5.0×10^6 cells/mL every 7 or 14 days, 0.5×10^6 cells/mL every 7 or 14 days, or to vehicle alone. A higher mean wound reduction was found with active treatment vs vehicle ($P = .0446$), with dose of 0.5×10^6 cells/mL every 14 days having the largest improvement 24-week follow-up to previous study (Kirsner et al ¹²⁷); 183 patients followed up every 8 weeks; 43% of HP802-247 treated patients vs 35% vehicle patients had closure, while 10% and 17% had reopening of a previously closed wound
Connexin 43	Topically applied gap junction protein-specific antisense-containing gel			Mendoza-Naranjo et al ¹⁶⁷ (2012)	No RCT available

Dermal					
Xenogenic					
Biobrane E-Z	Acellular porcine collagen type I	<ul style="list-style-type: none"> • Translucent • Long shelf life • Elastic • Immediately available 	<ul style="list-style-type: none"> • Expensive • Possible bovine allergy • May need multiple applications 	Barber et al ¹¹⁴ (2008)	Systematic review
Oasis	Porcine intestinal collagen and extracellular matrix	<ul style="list-style-type: none"> • Long shelf life • Cost effective • Stored at room temperature 	<ul style="list-style-type: none"> • Applied weekly • Possible bovine allergy 	Romanelli et al ¹²⁰ (2010)	<p>RCT: 55 patients received OASIS or petrolatum-impregnated gauze for 8 weeks. OASIS wounds healed faster than control group ($P = .02$), and had more complete wounds ($P < .05$), faster time to dressing change, and percentage of granulation tissue formed ($P < .05$)</p> <p>Systematic review</p>
Integra	Bovine tendon collagen and shark chondroitin	<ul style="list-style-type: none"> • Stored at room temperature • Flexible • Immediately available 	<ul style="list-style-type: none"> • Requires multiple applications 	<p>O'Donnell Jr and Lau¹¹⁹ (2006)</p> <p>Plotner and Mostow¹²¹ (2010)</p> <p>Mostow et al¹¹⁷ (2005)</p>	<p>No RCT</p> <p>RCT; 120 patients assigned to receive SGS plus compression therapy vs compression therapy alone for ≤ 12 weeks. 55% of SGS vs 34% of compression group healed ($P = .196$)</p> <p>No RCT available</p>
Dermal					
Allogenic					
Dermagraft	Neonatal foreskin fibroblast on a biodegradable mesh	Single application		<p>Harding et al¹²⁸ (2013)</p> <p>Omar et al¹⁰⁹ (2004)</p> <p>Landsman et al¹²⁹ (2011)</p>	<p>RCT; 186 patients assigned to Dermagraft plus compression therapy vs compression therapy alone over 12 weeks; 34% of Dermagraft patients had healing vs 31% in control group ($P = .235$); complete healing observed in 57% of Dermagraft group vs 39% in control group ($P = .223$)</p> <p>No RCT available</p> <p>No RCT available</p>

Continued

Table VIII. Cont'd

Name	Description	Advantage	Disadvantage	Study	Study outcome
HAM	Inner layer of the amniotic sac, cryopreserved for transplantation	<ul style="list-style-type: none"> Nonimmunogenic Low cost 	<ul style="list-style-type: none"> Long healing time Unstratified epithelium—may be an obstacle for migration of keratinocytes Closely resembles cutaneous basement membrane (ie, amniotic epithelium is at risk of being replaced by a reconstructed epidermis) Does not survive in chronic wounds after 2-4 weeks 	Tauzin et al ¹³⁰ (2011) Mermet et al ¹³¹ (2007) Gutierrez-Moreno et al ¹³² (2011) Alsina-Gibert and Pedregosa-Fauste ¹³³ (2012) Pesteil et al ¹³⁴ (2007)	No RCT available No RCT available No RCT available No RCT available No RCT available
DCD	Cadaveric tissue skin with all epidermal and cellular components of the dermis removed	<ul style="list-style-type: none"> Applied without immobilization Single application 		Greaves et al ¹²³ (2013)	No RCT available
Composite					
Xenogenic and allogenic					
Apligraft	Neonatal foreskin keratinocyte and fibroblast bilayered with bovine collagen	<ul style="list-style-type: none"> Self-repair ability Single application Stored at room temperature Immediately available 	<ul style="list-style-type: none"> Expensive Minimal shelf life 	Karr ¹²⁴ (2011) Serena and Bialas ¹³⁵ (2009) O'Donnell et al ¹¹⁹ (2006) Plotner and Mostow ¹²¹ (2010) Landsman et al ¹²⁹ (2011)	No RCT available Case report Systematic review No RCT available No RCT available
Dermal artificial grafts					
Xenogenic					
Biobrane	Inner nylon mesh coated with porcine type I collagen attached to silicone membrane	Long shelf life	<ul style="list-style-type: none"> Expensive Possible bovine allergy May need multiple application Minimal shelf life 	Barber et al ¹¹⁴ (2008)	Systematic review
PriMatrix	Fetal bovine dermis with type I and III collagen	Long shelf life		Karr ¹²⁴ (2011)	No RCT available

Allogenic					
Hyalomatrix PA	A total ester derivative of hyaluronic acid, made of HYAFF* and coupled with medical grade silicone	<ul style="list-style-type: none"> • Immediate availability • User-friendly application 	Daily topical administration	Motolese et al ¹³⁶ (2013) Plotner and Mostow ¹²¹ (2010)	No RCT available No RCT available
CGS impregnated with bFGF	Collagen/gelatin sponge (CGS) with a 10 wt% concentration of acidic gelatin that releases positively charged growth factors for 10+ days <i>in vivo</i>	<ul style="list-style-type: none"> • Sustains and releases bFGF in a controlled manner • Applied less frequently than other growth factors 		Morimoto et al ¹³⁷ (2013)	RCT; 17 patients were assigned to CGS impregnated with bFGF with 7 or 14 µg/cm ² after debridement and assessed after 28 days; wounds improved in 16 patients; no significant difference seen between groups
TheraSkin	Cryopreserved human skin allograft within 24 hours of death	Minimally processed to preserve native components of real human skin		Landsman et al ¹²⁹ (2011)	No RCT available
Skin grafts					
Pinch grafts	A small graft of skin, obtained by elevating the skin with a needle and excised from the base	<ul style="list-style-type: none"> • Readily obtained 	<ul style="list-style-type: none"> • Successful closure may require multiple attempts • End result can have cobblestone appearance 	Jones et al ¹³⁸ (2013) Jones et al ¹¹³ (2007)	No RCT available No RCT available
Split thickness graft	<ul style="list-style-type: none"> • Consists of epidermis and a portion of the dermis • Conform easily to irregular wound beds • Donor site can be reharvested 	<ul style="list-style-type: none"> • Easily expands 	<ul style="list-style-type: none"> • End result can have cobblestone appearance • Become hypo- or hyperpigmented • Have decreased thickness, which limits use 	Ross et al ¹³⁹ (2011), NPWT and grafts Høgsberg et al ¹⁴⁰ (2011)	No RCT available No RCT available

bFGF, Basic fibroblast growth factor; CGS, collagen/gelatin sponge; *DCD*, decellularized dermis; *HAM*, human embryonic membrane; *NPWT*, negative pressure wound therapy; *RCT*, randomized controlled trial.

*HYAFF is manufactured by Anika Therapeutics (Bedford, MA).

Phlebectomy and sclerotherapy have been performed for the treatment of varicose tributaries.⁹³ A systematic review and metaanalysis found 11 studies of surgical therapy versus conservative therapy in the management of VLUs.⁹⁵ The current study concluded that surgical intervention may improve the healing of VLUs, but cautioned that the quality of the available evidence is low.⁹⁵

Incompetent perforator veins

Patients with CVI are commonly found to have enlarged perforator veins with incompetent valves that allow reversal of flow from the deep venous system into the superficial system. The increased pressure transmitted into the superficial system contributes to inflammation and ulceration. Subfascial endoscopic perforator surgery (SEPS), a surgical technique to correct incompetent perforators, has been successful in multiple studies. In a metaanalysis comparing SEPS to the traditional Linton procedure (ie, ligation of all the perforating veins from ankle to proximal calf), the former was found to reduce the rate of VLU recurrence, secondary infection, and duration of hospital stay.⁹⁶⁻⁹⁸ Nelzen et al⁹⁹ found that SEPS of the superficial long saphenous vein was associated with less recurrence and positive long-term outcomes. Olivencia¹⁰⁰ reported that 79% of patients had a healing time of 2 to 3 months after SEPS.

In recent years, percutaneous methods to ablate incompetent perforators using laser or radiofrequency energy have emerged and have generally replaced SEPS in many venous practices. Percutaneous methods have the advantage of performance under local anesthesia with minimal morbidity.¹⁰¹ Success rates have been reported at 60% to 80% for an individual procedure, with 90% of perforators closed with multiple attempts. Early reports suggest benefit in improving ulcer healing, but data are limited.¹⁰¹⁻¹⁰³

Superficial venous ablation

Minimally invasive surgeries, such as superficial venous sclerotherapy or ablation, have been used in the management of patients with VLUs.^{104,105} Less invasive methods improve healing of VLUs with isolated superficial incompetence.³ In a series reported by Pang et al,⁹⁰ VLUs were treated with ultrasound-guided foam sclerotherapy combined with compression therapy.⁹⁰ Combined therapy led to 81% healing at 6 months and 5% recurrence at 2 years.

Venous compression syndromes

Patients with recalcitrant VLUs may present with compression of the iliac venous system or vena cava

(May-Thurner syndrome [MTS]). In a review of 75 consecutive patients with VLUs, significant compression of the venous outflow tract was documented in 37%.^{101,106} These patients may require venous intervention.

Obstruction of the venous outflow tract results in increased venous pressure, particularly with ambulation. This obstruction is a primary cause of poor adherence to compression therapy. Ambulation in a patient with MTS results in limb engorgement, leading to pain in the leg being treated with high-strength compression. Percutaneous stenting of the obstructed vein results in improved venous drainage, reduced limb edema, and pain alleviation. There is no current evidence that venous stenting results in improved ulcer healing or reduced recurrence.¹⁰⁷

USE OF ADJUNCTIVE THERAPIES: WHEN AND WHY

Key points

- If a healable venous leg ulcer does not heal despite good standard treatment, adjunctive therapies should be considered
- Adjunctive therapies include skin grafts and bioengineered skin, growth factors, and electrostimulation therapy

VLUs that have the ability to heal yet remain “stalled” despite good standard treatment disrupt the activities of daily life of the patient and increase costs.

Skin graft and bioengineered skin

Pinch graft and split-thickness grafts both have been successful in the treatment of patients with VLUs (Table VIII).^{69,108-110} Some studies report 50% healing after mesh skin grafting.^{111,112} However, limited data exist from RCTs. A Cochrane review supports bilayer artificial skin grafts for healing of refractory VLUs.¹¹³ A systematic review by Barber et al¹¹⁴ showed the importance of the dermal component in addition to the epidermal component in the improvement of venous ulcer healing rate. A bilayered skin equivalent (BSE; Apligraf, Organogenesis, Canton, MA) is the only skin equivalent therapy approved by the FDA for the treatment of VLUs.^{115,116} BSE is an allogeneic cultured bilayer skin construct derived from neonatal foreskin. It has a dermal layer comprised of human fibroblasts in a bovine type 1 collagen matrix, combined with an epidermal component of human keratinocytes. Data from a single RCT have shown that BSEs are effective for refractory VLUs and diabetic foot ulcers.¹¹⁶ Porcine small intestine submucosa (OASIS Wound Matrix; Healthpoint Ltd,

Table IX. A review of literature on use of growth factors in the management of venous leg ulcers (2004-2014)^{99,123,124,130,134-141,146-149,163-165}

Name	Description	Study	Study outcome
Autologous platelet-rich fibrin matrix membrane	Natural fibrin matrix obtained from autologous peripheral blood	O'Connell et al ¹⁵⁰ (2008)	No RCT available
Platelet gel/platelet-rich plasma	Hemocomponent obtained in vitro by pairing concentrated platelets with calcium chloride and thrombin to form a fibrin clot	Ficarelli et al ⁶⁰ (2008) Park et al ⁶¹ (2013) De Leon et al (2011) ¹⁶³ Frykberg et al (2011) ¹⁶⁴	No RCT available No RCT available No RCT available No RCT available
Granulocyte/macrophage colony-stimulating factor	Man-made form of granulocyte/macrophage colony-stimulating factor that is an hematopoietic growth factor and immune modulator	Cianfarani et al ¹²⁵ (2006) Da Costa et al ¹⁶⁵ (1999) Brem et al ¹¹⁶ (2008)	No RCT available Systematic review (no RCT) No RCT available
Basic fibroblast growth factor	A fibroblast growth factor	Seidman et al ¹⁴⁶ (2006)	No RCT available
Vitronectin: growth factor	Sterile combination of recombinant vitronectin, IGFBP-3, IGF-I, and EGF delivered in a solution comprised of disodium hydrogen phosphate, potassium dihydrogen phosphate sodium chloride, and potassium chloride	Upton et al ¹⁴⁷ (2011)	No RCT available
Platelet-derived growth factor	Platelet-derived growth factor is a protein commonly released by degranulating platelets, macrophages, endothelial cells, fibroblasts, and keratinocytes in the wound healing cascade	Trent et al ¹⁴⁸ (2005) Mwaura et al ¹⁴⁹ (2006) Margolis et al ¹⁵¹ (2009)	No RCT available No RCT available Phase I clinical trial; 15 patients received platelet-derived growth factor injections and were monitored over 24 weeks; 93% of patients had a decrease in wound size; 2 patients healed by day 28; 47% of patients healed at 24 weeks of follow-up
Calcitonin gene-related peptide and vasoactive intestinal polypeptide	Potent vasoactive and antiinflammatory peptide	Gherardini et al ¹⁶⁶ (1998)	66 patients were assigned to either standard treatment plus iontophoresis of calcitonin gene-related peptide and vasoactive intestinal polypeptide, or standard treatment plus placebo iontophoresis for 12 weeks; the results showed a surface area reduction of 74% in the treatment group vs 44% in the control group ($P < .05$), and complete healing was seen in 11 treatment patients vs 6 control patients ($P < .05$)

EGF, Epidermal growth factor; IGF-I, insulin-like growth factor; IGFBP-3, insulin-like growth factor binding protein 3; RCT, randomized controlled trial.

Fort Worth, TX) accelerates healing of VLUs.¹¹⁷ In a study by Mostow et al,¹¹⁷ a total of 120 patients with VLUs were randomized to receive either weekly topical treatment of small intestine submucosa (SIS) plus compression or compression therapy alone. After 12 weeks, 55 % of wounds treated with SIS healed versus 34% in the control group ($P=.01$).¹¹⁷ A review of the literature on the use of artificial skin substitutes, including acellular matrix, is listed in Table VIII.^{109,113,114,117-124,128-141}

Growth factors

Granulocyte monocyte colony stimulating factor has been delivered by intralesional injection to accelerate VLU healing.¹⁴²⁻¹⁴⁴ Other growth factor delivery mechanisms exist, such as autologous platelet-rich plasma. Although case series have suggested that platelet-rich plasma may be used in the treatment of VLUs, evidence from RCTs have shown no significant benefit compared to standard care.¹⁴⁵ A review of evidence on the use of growth factors in the management of VLUs is listed in Table IX.^{7,60,61,125-127,146-151}

Electrostimulation therapy

Evidence for the use of electrostimulation therapy (EST) in the management of patients with VLUs is limited. On the whole, evidence for EST is limited. Jankovic et al¹⁵² noted improved healing in 35 patients treated with EST. However, a Cochrane review identified no statistically significant improvement of healing with EST compared to sham therapy.¹⁵³

Negative pressure wound therapy

A 2008 Cochrane review reported no beneficial effect of negative pressure wound therapy (NPWT) for the healing of VLUs.¹⁵⁴ However, NPWT has been used to promote granulation tissue before skin grafting.¹⁵⁵ Since the Cochrane review, Dini et al¹⁵⁶ reported that NPWT accelerates granulation tissue formation clinically and used immunohistochemical evaluation to demonstrate improved angiogenesis (CD31), lymphatic vessel formation (D240), and macrophage (CD68) and lymphocyte (CD3) proliferation after 1 week of therapy. Armstrong et al¹⁰⁴ found an ultraportable mechanically powered NPWT device to be equally efficacious to an electrically powered device in VLU management with less impact on daily activities, mobility level, social interactions, and sleep.¹⁵⁷

Other treatments

Low frequency (<100 kHz), low intensity (<100 mW/cm²) lasers have been used in the

management of patients with VLUs.¹⁵⁸ Increased cellular metabolism and subsequent cell proliferation were identified in the wounds exposed to laser therapy.^{158,159} Caetano et al¹⁶⁰ used phototherapy as an adjunctive therapy in the management of 20 patients with VLUs. A 2010 Cochrane review did not support that either lasers or phototherapy facilitates the healing of VLUs.¹⁶¹

In conclusion, VLUs are a growing health care burden. Dermatologists require the skills to diagnose, assess, treat, and prevent venous disease. Venous disease management can be optimized by treating pain and infection, reducing the bioburden, and through the routine use of compression therapy. The use of adjunctive systemic agents, skin grafting, biologic therapies, or venous intervention may promote healing in patients with refractory VLUs.

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Coagulation disorders and their cutaneous presentations: Pathophysiology

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Learning Objective

After completing this learning activity, participants should be able to accurately describe the etiopathogeny of coagulopathies to accurately identify the associated cutaneous manifestation.

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Hypercoagulable states are inherited or acquired predispositions to venous or arterial thromboses that are best understood in the context of the coagulation cascade. Dermatologists can play a critical role in diagnosing and treating patients with hypercoagulable states because cutaneous symptoms may be a presenting manifestation, thereby reducing morbidity and mortality related to these conditions. This review focuses on the epidemiology and pathophysiology of hypercoagulable states, while the accompanying article iterates the basic clinical features, diagnostic testing, and management of patients who have these conditions. (J Am Acad Dermatol 2016;74:783-92.)

Key words: antiphospholipid syndrome; antithrombin; coagulation cascade; cryoglobulinemia; factor V Leiden; hypercoagulable state; hyperhomocysteinemia; protein C; protein S; prothrombin; sickle cell disease.

Given that the skin is often the initial presentation for intravascular thromboses, dermatologists play a key role in early diagnosis, focused work-up, and treatment of these conditions. This is important because thrombotic events manifested by venous thromboembolism (VTE), such as deep vein thrombosis (DVT), pulmonary embolism (PE), and arterial thrombosis, including acute coronary syndrome, stroke, and peripheral claudication, are a major cause of morbidity and mortality.^{1,2} A recent study noted a 4-fold increased risk of death in patients with venous thrombosis compared to controls that persists up to 8 years after the thrombotic event.¹

As a component of the Virchow triad, hypercoagulability is a risk factor for thrombotic events.³⁻⁶ Understanding the coagulation cascade offers insight into the pathophysiology of venous and arterial thromboses for patients with inherited and acquired forms of hypercoagulable states (HSs; **Table I**).

COAGULATION CASCADE

Key points

- **Hemostasis, regulated by both the extrinsic and intrinsic pathways of the coagulation cascade, is a host mechanism in place to protect the vascular system**

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Abbreviations used:

APC:	activated protein C
APS:	antiphospholipid syndrome
ATIII:	antithrombin III
ATIIID:	antithrombin III deficiency
DVT:	deep vein thrombosis
FVLM:	factor V Leiden mutation
HCV:	hepatitis C virus
HH:	hyperhomocysteinemia
HIT:	heparin-induced thrombocytopenia
HS:	hypercoagulable state
PE:	pulmonary embolism
PT/INR:	prothrombin time/international normalized ratio
TF:	tissue factor
TM:	thrombomodulin
TPP:	thrombotic thrombocytopenic purpura
VTE:	venous thromboembolism
VWF:	von Willebrand factor
WISN:	warfarin-induced skin necrosis

- **Hemostasis is a complex balance of prothrombotic and antithrombotic factors and provides a basis for understanding inherited and acquired hypercoagulable states**

After injury, a normally quiescent cascade of anti- and procoagulant factors becomes activated, producing the platelet plug and fibrin-based clot necessary to protect the integrity of the vascular system. The physiologic extrinsic and intrinsic coagulation pathways (Fig 1) are the 2 converging networks involved in this process, mediated by sequentially activated plasma serine proteases and cofactors. Inflammatory and repair processes, including the deposition of white blood cells at the injured site, are also part of this complex host defense mechanism.^{7,8}

The extrinsic pathway is the major pathway in driving coagulation. Exposure of tissue factor (TF) on damaged endothelial cells to circulating factor VII (FVII) leads to autoactivated FVIIa.⁹ The FVIIa–TF complex cleaves factor X (FX) into its active form (FXa). It is important to note that FXa is a key enzyme in both the extrinsic and intrinsic pathways. Afterward, FXa associates with factor V (FV) to form prothrombinase, which converts prothrombin to thrombin. Thrombin in turn cleaves fibrinogen to form fibrin, thereby initiating the clot.⁷

The intrinsic pathway is triggered by activation of the contact system, involving FXII, FXI, plasma kallikrein (PK), and high molecular weight kininogen (HMWK). FXII and HMWK make contact with negative charges underlying the injured endothelium, which activates FIX to FIXa. FIXa, with its cofactor VIII (FVIII), activates FX to FXa, resulting in thrombin production and clot formation.⁸

Table I. Inherited and acquired hypercoagulable states

Inherited (or primary)	Acquired (or secondary)
Factor V Leiden mutation	Heparin-induced thrombocytopenia
Antithrombin III deficiency*	Warfarin-induced skin necrosis
Protein C deficiency*	Antiphospholipid syndrome
Protein S deficiency*	Thrombotic thrombocytopenic purpura
Prothrombin G20210A mutation	Cryoglobulinemia
Hyperhomocysteinemia*	Cryofibrinogenemia
Sickle cell disease	Immobilization
	Obesity
	Cancer
	Pregnancy
	Other (eg, medications, surgery)

*May also be acquired.

Coagulation is balanced at 3 levels. First, thrombin changes into an anticoagulant factor upon binding with thrombomodulin (TM), an endothelium-bound glycoprotein; this complex loses the ability to clot fibrinogen. The thrombin–TM complex allows rapid cleavage and production of activated protein C (APC), which binds to its cofactor protein S on endothelial or platelet surfaces. This complex downregulates further thrombin formation by proteolytically inactivating FV and FVIII. Secondly, circulating proteinase inhibitors, including tissue factor pathway inhibitor (TFPI), C1 inhibitor, and antithrombin III (ATIII), inactivate coagulation factors to prevent expansion of clotting adjacent to the damaged tissue (Fig 1).^{8,10-12} Finally, thrombin-dependent activation of thrombin-activatable fibrinolysis inhibitor (TAFI) hinders fibrinolysis inside the clot. Homeostatic imbalances in these pro- and anticoagulant factors lead to excess bleeding or thrombosis.

INHERITED HYPERCOAGULABLE STATES

Key points

- **Multiple inherited hypercoagulable states exist, which increase the risk of thromboses through multiple mechanisms**
- **Factor V Leiden mutation is the most common inherited hypercoagulable state**

FACTOR V LEIDEN MUTATION

Factor V Leiden mutation (FVLM) is the most common primary HS, occurring in 5% to 15% of the population.¹³ Approximately 5% of whites are

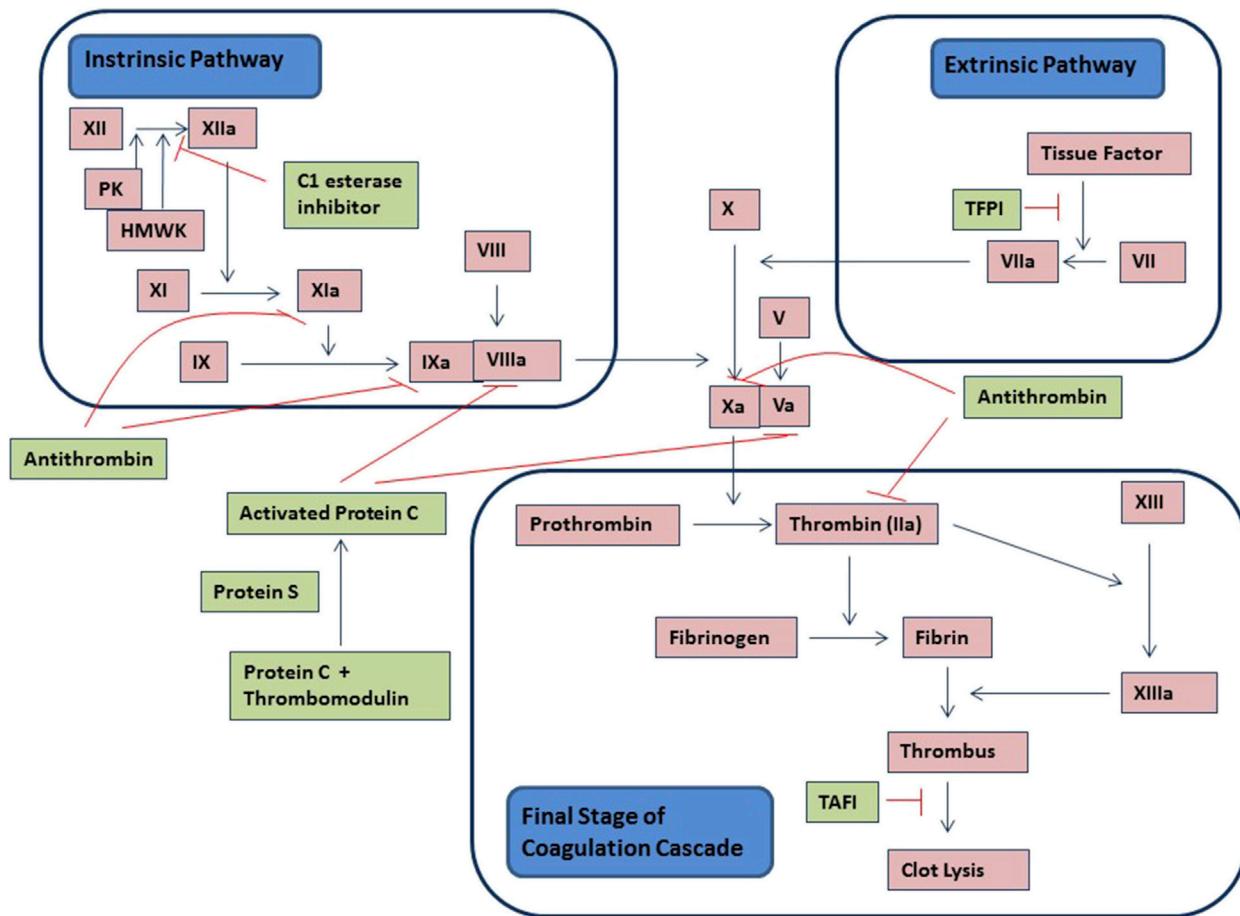


Fig 1. Extrinsic and intrinsic coagulation pathways. HMWK, High-molecular-weight kininogen; TAFI, thrombin-activatable fibrinolysis inhibitor; TFPI, tissue factor pathway inhibitor.

heterozygous for FVLM, and it is rarely seen in other ethnic groups.¹³ FVLM is an autosomal dominant disorder caused by a point mutation in the gene for FV, switching a guanine to adenine and replacing arginine-506 to glutamine-506 (Arg506Gln) in 1 of the 3 APC cleavage sites. Physiologically, FV functions as a cofactor of FXa, leading to activation of thrombin, and is normally cleaved and degraded by APC. In FVLM, the mutant FVa is resistant to degradation by APC, and the coagulation cascade remains activated for longer than normal, with subsequent overproduction of thrombin and excess fibrin.^{14,15} The risk of primary and recurrent VTE is increased by 3- to 6-fold with heterozygous mutation^{13,16} and 30- to 140- fold with homozygous mutation.¹⁷ Other thrombotic manifestations reported include cerebral, mesenteric, portal vein, and postsurgical thrombosis, as well as pregnancy loss.¹⁸

Prothrombin G20210A mutation

Prothrombin G20210A mutation is the second most common primary HS. It is present in

approximately 1.1% to 3% of the general population¹⁹⁻²¹ and increases the risk of venous thrombosis by 3-fold.¹⁷ It is an autosomal dominant mutation in the 3' untranslated region at nucleotide 20210 of the prothrombin gene. A guanine to adenine substitution leads to elevated circulating plasma levels of prothrombin with subsequent increased thrombin formation.²²

Antithrombin III deficiency

ATIII is a multifunctional member of the serpin family of serine protease inhibitors, synthesized predominantly in the liver with a half-life of approximately 2.4 days.²³ It is a natural anticoagulant protein that inactivates multiple coagulation factors, including thrombin (FIIa) and FXa, and to a lesser extent FIXa, FXIa, and FXIIa.

Antithrombin III deficiency (ATIID) is an uncommon autosomal dominant disorder reported to occur in <0.02% to 0.2% of the general population and 3% to 5% of patients with thrombotic disease.²⁴⁻²⁶ The ATIII gene is located on chromosome 1q23-25, and >130 different mutations in the ATIII gene have been

reported.²⁷ Most mutations are heterozygous and are divided into 2 types. Type I is a quantitative deficiency caused by low levels of anticoagulant protein. Type II is qualitative, in which normal amounts of antithrombin exist but function improperly.²⁷ For example, there may be mutations in the heparin- or thrombin-binding sites. Homozygous ATIID is rare and nearly always fatal in utero.

Of note, ATIID may be acquired by several mechanisms, commonly by increased consumption of ATIII because of increased coagulation (ie, disseminated intravascular coagulation, severe injury/trauma, cardiopulmonary bypass, or microangiopathic hemolytic anemia), endothelial damage (ie, hemolytic-uremic syndrome), or venoocclusive disease in patients who have undergone bone marrow transplant.²⁸ Cases of synthetic failure occur because of chronic liver disease, whereas protein loss occurs secondary to nephrotic syndrome, ascites, or protein-losing enteropathy. Medications can cause acquired disease via procoagulant effects (ie, heparin-induced thrombocytopenia) or by nonspecific impairment of protein synthesis (ie, l-asparaginase).^{23,28}

Protein C and protein S deficiencies

Protein C and protein S deficiencies are autosomal dominant genetic traits characterized by numerous heterozygous mutations. Heterozygous protein C deficiency is present in an estimated 0.2% to 0.5% of the general population and 2% to 5% of patients presenting with VTE.²⁹⁻³¹ Heterozygous protein S deficiency is present in <0.1% to 0.3% of the population.³¹ They are also classified as quantitative (type I) or qualitative (type II) deficiencies. As explained above, APC combines with protein S on the platelet surface to inactivate FVa and FVIIa. Low levels or functional impairment in either protein causes an unbalanced activation of FVa and FVIIa, resulting in increased thrombin production and clot burden.

Acquired protein C or S deficiency occurs in patients with liver disease because of synthetic failure, vitamin K deficiency, warfarin use, pregnancy, sex hormone therapy, and certain chronic infections, such as HIV.³²

Hyperhomocysteinemia

Homocysteine is a sulfhydryl-containing amino acid formed during methionine metabolism, and elevated serum levels confer an increased risk of both venous and arterial thrombosis.³³ Inherited hyperhomocysteinemia (HH) stems from mutations in homocysteine pathway enzymes. Commonly, a

cytosine to thymine missense mutation at nucleotide 677 substitutes valine for alanine in the methyltetrahydrofolate reductase (MTHFR) gene, resulting in a hypofunctioning thermolabile variant and elevated homocysteine levels.³⁴ Less commonly, HH results from mutations in cystathione-β-synthase, the enzyme deficiency in congenital homocystinuria.³⁵ HH confers an increased risk of cardiovascular events^{35,36} and a 2- to 4-fold increase in the relative risk of developing venous thrombosis; when coexpressed with FVLM, the relative risk increases to 20-fold.³⁷ Acquired HH is caused by renal or thyroid disease, smoking, aging, and vitamin B₁₂, B₆, or folate deficiency.

It remains unclear how HH promotes thrombosis, but several studies implicate endothelial dysfunction, including impaired endothelium-dependent regulation of vascular tone and blood flow, increased recruitment of inflammatory mediators, and a loss of endothelial cell antithrombotic function. Increased vascular oxidant stress through the inhibition of key antioxidant enzymes and imbalanced redox status is central in these molecular mechanisms.^{38,39}

Sickle cell disease

Sickle cell disease includes a group of autosomal recessive hemolytic anemias caused by a single nucleotide mutation substituting valine for glutamic acid at the sixth position of the β-hemoglobin gene, causing subsequent polymerization of hemoglobin when deoxygenated with formation of hemoglobin S.⁴⁰ Acidosis or hypoxia leads to abnormal polymerization of hemoglobin tetramers and formation of sickled erythrocytes that are less flexible, prone to hemolysis, and adherent to the endothelium.⁴⁰ Erythrocytes become lodged within smaller vessels, causing vascular obstruction, ischemia, and tissue necrosis. In addition, studies suggest that activation of coagulation is a prominent feature of sickle cell disease, as evidenced by increased TF expression, increased coagulation activation markers (including prothrombin fragment 1.2 and thrombin:antithrombin complexes^{41,42}), the depletion of natural anticoagulant proteins, and abnormal fibrinolysis.^{40,43,44}

ACQUIRED HYPERCOAGULABLE STATES

Key points

- **Acquired causes of hypercoagulable states include medications, protein-induced diseases, and broader systemic illnesses**
- **A good history and high degree of suspicion for an acquired hypercoagulable state is necessary to diagnose and treat appropriately**

Warfarin-induced skin necrosis

Warfarin is a commonly used anticoagulant that inhibits the synthesis of vitamin K-dependent clotting factors, including FII, FVII, FIX, and FX, as well as proteins C and S. Warfarin-induced skin necrosis (WISN) or, less commonly, warfarin-induced venous limb gangrene, are rare complications occurring in 0.01% to 0.1% of warfarin users.⁴⁵ The mechanism is hypothesized to be caused by the distinct half-life of mediating factors. Protein C has a shorter half-life (6–8 hours) than other clotting factors and is depleted earliest within the first few days of therapy, before FX and FII disappear (half-lives of 2–5 days). This results in relative hypercoagulability during the initial 24 to 72 hours of warfarin therapy,⁴⁶ which may lead to thrombosis and subsequent skin necrosis if warfarin is initiated without an adequate heparin bridge. Risk factors for WISN include protein C, protein S, FVL, and ATIII deficiencies,^{47,48} heparin-induced thrombocytopenia (HIT), and malignancies.⁴⁹ Clinically, the prothrombin time (PT) or international normalized ratio (INR) is used to evaluate the therapeutic efficacy of warfarin. PT/INR is highly dependent on FVII, which also has a short half-life (4–6 hours), and therefore allows misleading therapeutic INR measurements during the hypercoagulable window.⁵⁰

Heparin-induced thrombocytopenia

HIT is an adverse drug reaction characterized by thrombocytopenia and increased risk of venous or arterial thrombosis. The frequency of HIT ranges from 1% to 5% of patients receiving heparin, differing between specific heparin agents.⁵¹ Two types of HIT have been described. Type I is a non-immune-mediated transitory, mild, and asymptomatic reduction in platelet count 1 to 2 days into therapy. Type II incurs a ≥50% decrease in platelets from baseline with thrombosis occurring 5 to 14 days after initiating therapy.⁵² HIT type II is caused by heparin-dependent immunoglobulin G (IgG) antibodies bound to platelet Fc gamma IIa receptors within the heparin/platelet factor 4 complex, leading to platelet activation and resultant clotting.⁵² The platelet count falls during this consumptive process, leading to thrombocytopenia.

Antiphospholipid syndrome

Antiphospholipid syndrome (APS) manifests as recurrent thromboses in the setting of acquired antibodies against various phospholipid-binding proteins, most commonly the lupus anticoagulant, anti-cardiolipin antibody, and anti-beta-2-glycoprotein-I antibody. Primary APS occurs without an underlying medical condition, whereas secondary APS is associated with autoimmunity, infection, malignancy, or

medications. Suggested mechanisms of thrombogenesis include complement activation, the activation of platelets via the p38MAPK/cPLA2 pathway, the activation of endothelial cells and monocytes through Toll-like receptor-4, annexin A2, and heparin sulfate moiety of the cell membrane, upregulation of TF and proinflammatory cytokines by the nuclear factor- κ B pathway,^{53,54} and impaired fibrinolysis.⁵⁵ APC resistance has been reported in patients with systemic lupus erythematosus and primary APS.⁵⁶

Thrombotic thrombocytopenia purpura

Normally, platelets adhere to ultralarge von Willebrand factor (VWF) multimers on exposed subendothelial connective tissue. The plasma protease ADAMTS13 cleaves VWF multimers within growing platelet aggregates to limit thrombus formation. Without ADAMTS13, platelet-rich microvascular thrombosis proceeds unchecked and TTP ensues.⁵⁷

TTP is inherited or acquired. Inherited TTP has absent or severely reduced plasma ADAMTS13 activity^{58,59} caused by homozygous or double heterozygous mutations in ADAMTS13 at multiple loci along the gene on chromosome 9q34.⁶⁰ Acquired TTP is caused by IgG autoantibodies targeting ADAMTS13. Reported associated medications include ticlopidine or clopidogrel.⁵⁷ HLA-DRB1*11 has been identified as a risk factor for acquired TTP.⁶¹

Cryoglobulinemia

Cryoglobulinemia is the presence of single or mixed immunoglobulins that alter in conformation and precipitate in the serum at a temperature below 37°C.⁶² The pathophysiology is poorly understood but is hypothesized to involve both vasculitic and vasculopathic processes. Cryoprecipitation results from reduced solubility of the IgM–IgG immune complex, which deposits on small vessel walls and activates the complement cascade. This results in plugging and thrombosis of small arteries and capillaries. Complement fragments, such as C3a and C5a, may act as chemotactic mediators of inflammation, with ensuing vasculitis.⁶³

Cryoglobulinemia is subcategorized into 3 groups according to immunochemical composition (Table II). Type I cryoglobulinemia (seen in 10–15% of cases) is composed of single monoclonal immunoglobulins, usually IgM, and is associated with lymphoproliferative disorders, such as Waldenström macroglobulinemia and multiple myeloma. Type I cryoglobulins rarely have rheumatoid factor activity and do not activate complement in vitro. Types II (50–60% of cases) and III (30–40% of cases) are composed of immune complexes of

Table II. Types of cryoglobulinemia

Cryoglobulins	Etiology	Clinical presentation
Type I—monoclonal immunoglobulins, usually IgM and less commonly IgG or IgA	Associated with hematologic malignancy, nephropathy, and neuropathy	Type I: Retiform, purpuric, or necrotic lesions at acral sites of cold exposure. Other cutaneous findings include acral cyanosis, Raynaud phenomenon, and livedo reticularis
Type II—polyclonal IgG and monoclonal IgM “mixed”	Mixed cryoglobulins are associated with chronic inflammation and infection, including hepatitis B and C viral infections,	Types II/III: Palpable purpura
Type III—polyclonal IgG and IgM “mixed”	systemic lupus erythematosus, rheumatoid arthritis, and Sjögren syndrome	

IgA, Immunoglobulin A; IgG, immunoglobulin G; IgM, immunoglobulin M.

polyclonal IgGs and monoclonal or polyclonal IgM, respectively, with rheumatoid factor activity.⁶⁴ They are associated with infections, namely viral hepatitis C (HCV), autoimmunity, and neoplastic diseases.⁶⁵ Cryoglobulinemia occurs in 30% to 50% of patients with chronic HCV, although only 10% to 15% of patients develop clinical symptoms.⁶⁴ HCV proteins may have a direct role in the pathogenesis of disease-related cases.^{66,67}

Cryofibrinogenemia

Cryofibrinogenemia is a rare disorder caused by a cryoprotein that precipitates only in the plasma and not in serum.⁶⁸ The substance is a cold, insoluble complex of fibrin, fibrinogen, and fibrin split products with albumin, plasma proteins, and immunoglobulins. Cryofibrinogen clots with thrombin and reversibly precipitates in the plasma on cooling to 4°C and redissolves on warming to 37°C. This precipitate leads to thrombotic occlusion of small and medium arteries.⁶⁹ It is most often associated with an underlying inflammatory disorder, infection, or malignancy, but familial primary cases with autosomal dominant inheritance have been described.⁷⁰ Cutaneous manifestations of vascular occlusion are common.⁷¹

Immobilization

Immobility increases thrombotic risk, presumably because of stasis of venous blood flow. Many factors contribute to immobility, including bed rest, long travel times, fractures, plaster casts, neuromuscular impairment, and surgery.⁷²

Obesity

Obesity is an important modifiable risk factor for thrombosis. Obesity imparts a 2- to 3-fold increased risk of VTE in both sexes.^{73,74} A recent metaanalysis suggests that abdominal obesity may be a stronger risk factor for VTE than body mass index.⁷⁵ Thrombosis risk in obesity is not significantly

mediated by differences in levels of fibrinogen, FVIII, FIX, or D-dimer.⁷⁴ However, obesity did correlate with increased thrombin generation, quantitative fibrinogen, and prothrombin levels in women with VTE.⁷⁶ Overall, additional investigations into these mechanisms are needed.

Cancer

Across all cancers, the risk of VTE is increased 7-fold, and in certain malignancies the risk is increased up to 28-fold.⁷⁷ Eighteen percent of all cases of incident VTE are cancer-related and caused by a combination of factors. Tumor cells activate coagulation through multiple mechanisms, including via procoagulant, fibrinolytic, and proaggregating activities, releasing proinflammatory and proangiogenic cytokines, and interacting directly with host vascular and blood cells through adhesion molecules. Increasing evidence suggests that elements of the hemostatic system have a direct role in eliciting or enhancing angiogenesis, cell survival, and metastasis.^{77,78}

Pregnancy

Pregnant women are at increased risk of both venous and arterial thromboses. Compared to nonpregnant women, the risk of arterial thromboembolism increases 3- to 4-fold,^{79,80} and the risk of VTE increases 4- to 5-fold (20-fold postpartum).⁸¹ VTE events are 4 times more frequent than arterial thromboses in pregnancy, 80% of which are DVTs (20% PEs).⁸²

Mechanisms are multifactorial, including hypercoagulability, hormone-induced decreased venous capacitance and outflow, mechanical obstruction by the uterus, and decreased mobility.⁸³ Normal pregnancy is accompanied by increased concentrations of procoagulant factors VII, VIII, X, VWF, and fibrinogen and decreased free protein S.^{84,85} Plasminogen activator inhibitor type 1 levels increase 5-fold, and markers of thrombin generation are

Table III. Drugs that may induce thrombosis

Drugs	Examples
Antipsychotics	First-generation antipsychotics (relative risk, 7): chlorpromazine, haloperidol, thioridazine, and zuclopentixol; second-generation antipsychotics (hazard ratio, 2): clozapine, olanzapine, quetiapine, risperidone, and ziprasidone
Chemotherapeutic agents	5-FU, all-trans-retinoic acid, bleomycin, busulfan, cis-platinum, doxorubicin, gemtuzumab, L-asparaginase, paclitaxel, tamoxifen, thalidomide, and VEGF antagonists, such as bevacizumab
Cocaine	
Contrast media	
Cyclooxygenase-2 inhibitors	
Ephedra	
Erythropoietin	
Granulocyte colony-stimulating factor	
Granulocyte-macrophage colony-stimulating factor	
Heparin	
Hormone replacement therapy, oral contraceptive pills	
Immunosuppressive agents	Cyclosporine, glucocorticoids, sirolimus, interferon-alfa, and intravenous immunoglobulin
Metformin	
Quinine	
Recombinant factor VIIa	
Selective serotonin reuptake inhibitors	
Sildenafil	
Thienopyridine derivatives	Ticlopidine and clopidogrel
Tissue plasminogen activator	
Tranexamic acid	

5-FU, 5-Fluorouracil; VEGF, vascular endothelial growth factor.

increased. These changes begin at conception and persist for ≥ 8 weeks postpartum.^{84,85} It has been suggested that hypercoagulability evolved to protect women from hemorrhage during childbirth.

Medications

Many drugs carry an increased risk of thrombosis, including warfarin and heparin (as described above), oral contraceptive pills, 5-fluorouracil, thalidomide analogs, antiangiogenic agents, and epidermal growth factor receptor inhibitors.⁸⁶ Table III summarizes drugs reported to induce thrombosis and the proposed mechanisms of action. Briefly, oral contraceptive pills are posited to increase thrombosis risk by increasing FVII, FX, plasminogen, and fibrinogen levels, as well decreasing antithrombin and protein S levels. This is balanced by an increase in fibrinolytic activity caused by a decrease in plasminogen activator inhibitor I. Thrombosis may ensue with local vascular wall damage or other risk factors, such as obesity,⁷⁴ older age, and smoking. Lower doses of estrogen are associated with the least change in hemostatic factors.^{87,88} 5-Fluorouracil causes endothelial damage by impairing antioxidant

defense capacity and generating the production of nitric oxide, a short-lived free radical. Free radicals increase lipid peroxidation and endothelial cell membrane damage with subsequent platelet aggregation.⁸⁹ Thalidomide and lenalidomide confer an increased risk of VTE, particularly when used in combination with high-dose dexamethasone.⁹⁰ The mechanism is likely multifactorial, including platelet activation, alterations in thrombomodulin,⁹¹ increased FVIII, and acquired resistance to APC.⁹² Additional mechanisms of drug-induced HSs are diverse and beyond the scope of this review.

In conclusion, there are many inherited and acquired forms of HSs that may be understood by appreciating the elements of the coagulation cascade. A good medical history, family history, and physical examination, especially for specific cutaneous manifestations, may suggest the presence of a HS. Factor V Leiden is the most common inherited HS, but clinicians must have a high index of suspicion for other conditions.

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Coagulation disorders and their cutaneous presentations: Diagnostic work-up and treatment

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Learning Objectives

After completing this learning activity, participants should be able to identify the indications for diagnostic testing for patients presenting with a cutaneous manifestation of an underlying coagulopathy and describe multidisciplinary treatment strategies for inherited and acquired coagulation disorders.

Disclosures

Editors

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Both inherited and acquired hypercoagulable states can present with nonspecific clinical manifestations, such as petechiae, purpura, livedo reticularis, and ulcerations. A good history and physical examination are crucial to diagnoses of these conditions. Inherited conditions tend to present either in neonatal period or later in life, while acquired conditions typically occur later in life. Diagnostic studies are performed to identify the coagulation cascade deficiency or defect. Treatment primarily hinges on anticoagulation and wound care. In this article, we provide an in-depth analysis of the clinical manifestations, diagnostic considerations, and management options of patients in hypercoagulable states. (*J Am Acad Dermatol* 2016;74:795-804.)

Key words: factor V Leiden mutation; hypercoagulable state; hyperhomocysteinemia; livedoid vasculopathy; protein C deficiency; protein S deficiency; thrombophilia; thrombosis; ulcers; warfarin necrosis.

The incidence of arterial and venous thromboses in patients in hypercoagulable states (HSS) is increased compared to the general population in spite of adequate preventive measures. In addition to macrovascular thromboses, HSS can lead to microvascular thrombi, leading to many nonspecific cutaneous manifestations, most notably ulcerations affecting the lower extremity (LE). However, ulcerations have many other causative etiologies that must be distinguished from a HS. Livedoid vasculopathy (LV) in the LEs is a major

distinguishing characteristic of patients with HSS. LV is characterized by recurrent reticulated purpura of the LEs with atrophie blanche (AB).¹ AB can be associated with LV, but also it can occur in the context of chronic venous insufficiency, further complicating the diagnostic picture. Many HSS have been linked to the development of LV (Table I). Here, we review the cutaneous manifestations of HSS and the vasculopathies most often encountered by the dermatologist in both the outpatient and inpatient settings.

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Abbreviations used:

AB:	atrophie blanche
APC:	activated protein C
APS:	antiphospholipid syndrome
AT:	antithrombin
ATIIIID:	antithrombin III deficiency
DVT:	deep vein thrombosis
ELISA:	enzyme-linked immunosorbent assay
FVL:	factor V Leiden
FVLM:	factor V Leiden mutation
HIT:	heparin-induced thrombocytopenia
HS:	hypercoagulable state
INR:	international normalized ratio
LE:	lower extremity
LMWH:	low molecular weight heparin
LV:	livedoid vasculopathy
PCR:	polymerase chain reaction
PT:	prothrombin time
PTT:	partial thromboplastin time
SCD:	sickle cell disease
TTP:	thrombotic thrombocytopenia purpura
VTE:	venous thromboembolism

Table I. Hypercoagulable states associated with livedoid vasculopathy*

Factor V Leiden mutation
Prothrombin G20210A mutation
Protein C and protein S deficiency
Antithrombin III deficiency
Hyperhomocysteinemia
Monoclonal cryoglobulinemia
Hepatitis B and C, related to polyclonal cryoglobulins
Cryofibrinogenemia
Antiphospholipid antibodies

*Adapted from Alavi et al.¹**CUTANEOUS MANIFESTATIONS OF HYPERCOAGULABLE STATES****Key points**

- Identifying the different cutaneous presentation of hypercoagulable states
- Identifying the histology of livedoid vasculopathy

Petechiae

Petechiae are pinpoint (≤ 3 mm), nonblanchable, erythematous macules that manifest as a result of erythrocyte extravasation from small cutaneous vessels. When nontraumatic, petechiae may herald thrombocytopenia, vasculitis, or concomitant anti-coagulant therapy. Traumatic petechiae may appear marked relative to the degree of injury if platelets are low or if there is aberrant hemostasis. However, petechiae can appear after trauma or an acute elevation in intravascular pressure with normal platelets and hemostasis.² No additional diagnostic tests are usually necessary to identify petechiae. In certain scenarios, obtaining a skin biopsy specimen may help rule out an occult vasculitis. Additional work-up for thrombocytopenia may be warranted.

Purpura

Purpura are nonblanchable, erythematous to violaceous macules or thin papules ranging in size from a few millimeters to several centimeters. Likewise, purpura imply erythrocyte extravasation from dermal or subcutaneous blood vessels.² The finding of “palpable purpura” is nondiagnostic, although palpable lesions are often indicative of a vasculitic disorder (Fig 1).^{3,4} Both hypo- and hypercoagulable states may present with purpura

and can generally be distinguished by the history, physical examination, and basic laboratory tests (eg, partial thromboplastin time/prothrombin time). Hypocoagulable states often manifest as nonpalpable purpura (eg, ecchymoses) occurring at sites of trauma. HS are heralded by the appearance of retiform purpura, or stellate-appearing purpura with an incomplete net-like vascular background.² The differential diagnosis for retiform purpura is broad but implies a systemic disease process causing microvascular occlusion, and a thorough work-up must ensue.⁵ A biopsy specimen of the skin may reveal features of vasculitis (ie, inflammation of vessel walls, erythrocyte extravasation, fibrinoid necrosis, or leukocytoclasia), vasculopathy (ie, vessel wall abnormalities without inflammation), or occlusion (ie, intraluminal thrombus or atherosclerosis).⁶ Purpura fulminans—purpuric lesions that enlarge and become vesiculated—produce hemorrhagic bullae with subsequent necrosis and black eschar formation.

Livedo reticularis

Livedo reticularis (LR) is an erythematous to violaceous, lacy, net-like, exaggerated venous pattern visible in states of slow venous flow (Fig 2). Classically, it presents on the lower extremities, is exacerbated in cold environments and, in idiopathic cases, reverses with warming the affected area, but once established the discoloration becomes permanent. Although LR may be a physiologic response to cold, in time LR may reflect an upstream occlusive process of arteries or arterioles, such as vasospasm or luminal obstruction (secondary LR). Neurologic disorders affecting vascular tone can also induce LR.^{2,6}

Systemic work-up in patients with LR is guided by the history and physical examination.^{3,7,8} The term livedo racemosa is used when the vascular patterns are fixed, the lacy pattern includes broken circles, and the patterns do not reverse with warming. This is considered an ominous sign of systemic disease.² A skin biopsy specimen obtained from the pale



Fig 1. Palpable purpura in a patient with positive lupus anticoagulant showing leukocytoclastic vasculitis on review of the biopsy specimen.

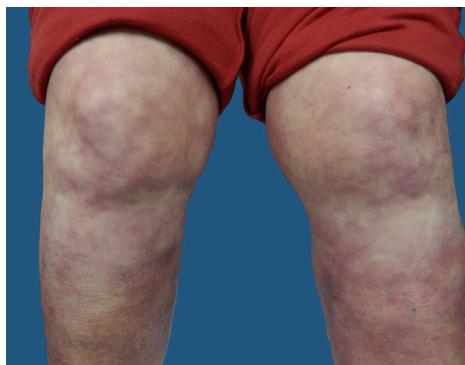


Fig 2. Livedo reticularis in a patient with systemic lupus erythematosus.

perilesional area may reveal changes of vasculopathy or vasculitis, sludging of erythrocytes, intraluminal thrombi, or arterial obliteration and provide insight into the underlying disease process.⁹

Livedoid vasculopathy

LV is a syndrome associated with hypercoagulability comprised of painful, punched out lower leg and foot ulcers on a background of LR or retiform purpura that heal with AB (ie, atrophic, stellate white scars bordered by telangiectasia and hemosiderin deposition; Fig 3).^{2,10} A diagnosis of LV compels a broad HS work-up and consideration of underlying connective tissue disease.^{1,11} Histologic features of nonulcerated skin classically include intraluminal thrombi and prominent hyalinization of vessel walls with scant perivascular inflammation (Fig 4).⁶ Direct immunofluorescence studies are frequently positive for fibrin, complement, and immunoglobulin deposition in dermal vessels.¹²



Fig 3. Atrophie blanche. Note the classic stellate white atrophic scars, telangiectasias, and hemosiderin deposition.

Ulcerations

Many primary and secondary HSs can manifest as ulcerations with features of venous or arterial origin. Venous leg ulcers typically appear in the “gaiter area” (ie, medial ankle to mid-calf), are shallow with fibrinous material overlying granulation tissue at the base, and have varying degrees of pain. There is often background pitting edema, venous varicosities, lipodermatosclerosis, and hemosiderin deposition. Chronic venous insufficiency can result from longstanding, recurrent superficial and deep venous thromboses associated with primary or secondary HS, and venous ulcers can be a manifestation of many HSs.^{4,11,13-17}

Arterial ulcers classically appear over the lateral malleoli or distal phalanges as painful, punched out ulcers with purpuric borders and prominent eschar.¹⁸ The affected limb may feature pallor and diminished arterial pulses. Upstream arterial occlusion can result from atherosclerosis, vaso-spasm, an underlying S, or a combination. Histology may implicate an underlying vasculitic or thromboembolic process; intraluminal clefts are seen in cholesterol emboli.⁶

Atypical nonhealing wounds, especially LE ulcers without venous or arterial insufficiency, should prompt work-up for an underlying HS, including cryoglobulinemia, cryofibrinogenemia, and anti-phospholipid syndrome (APS).^{4,19,20} Calciphylaxis may cause chronic, painful ulcers in patients with an underlying HS, with or without renal failure.²¹ Calcification and secondary thrombosis of dermal and subcutaneous small- and medium-sized vessels are seen on wedge biopsy.²²

INHERITED DISORDERS

Key points

- Hypercoagulable states can be inherited or acquired
- Homozygous mutations can cause purpura fulminans in the neonatal period and can be lethal

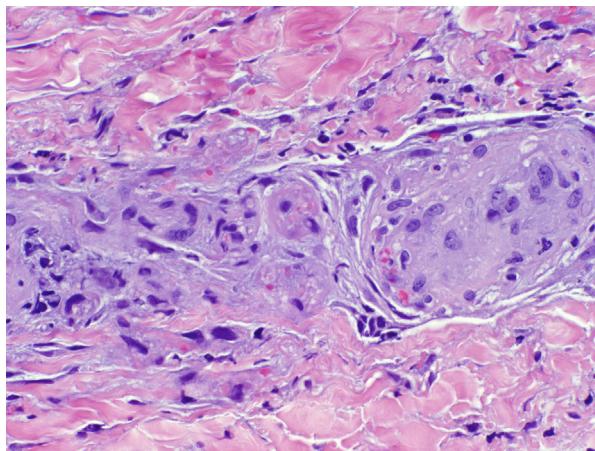


Fig 4. Livedoid vasculopathy revealing hyalinized dermal blood vessel walls with focal perivascular lymphohistiocytic infiltrate and intraluminal thrombus. (Hematoxylin–eosin stain.)

- Heterozygous mutations result in milder disease presentation
- Atrophie blanche is a common presentation of livedoid vasculopathy

Factor V Leiden mutation

Presentation. FVLM may be associated with any of the nonspecific cutaneous findings listed above, including LV. Cutaneous presentations of FVLM usually occur later in life. If a patient experiences their first thromboembolic event before 50 years of age and has an ulcerative skin lesion, then FVLM should be considered.²³

Laboratory tests. In a patient presenting with the clinical features described above, in addition to testing for FVLM, a hypercoagulation panel should be performed (Table II). A polymerase chain reaction (PCR)–based assay is used to determine whether FVLM is present. A perilesional skin biopsy can be performed with a narrow and long elliptical excisional biopsy specimen including the reticular dermis and subcutaneous tissue.²⁴ An ultrasound to rule out a deep vein thrombosis (DVT) is important if a patient presents with asymmetric LE edema.

Treatment. In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended for patients with an asymptomatic FVLM. In the presence of acute thrombosis, warfarin therapy should be initiated with a goal international normalized ratio (INR) of 2 to 3 for 3 to 6 months, with an initial bridging with heparin.²⁵ Decisions regarding the duration of anticoagulation are based on an individualized assessment of the risks for venous thromboembolism (VTE) recurrence and anticoagulant-related bleeding.²⁵ Routine preoperative screening for FVLM or any other thrombophilia

is not recommended. However, patients with known thrombophilia should be managed perioperatively with prophylactic anticoagulation.²⁶ There is no evidence that early diagnosis reduces morbidity or mortality, so decisions regarding testing at-risk family members should be made on an individual basis. Individuals with recurrent thrombosis at an early age with a family history of FVLM should be evaluated because they may need lifelong anticoagulation.²³ When cutaneous ulcerations are present, one should adhere to the basic principles of proper wound care. This includes optimizing granulation tissue formation, decreasing the bacterial burden, decreasing the inflammatory response, and maintaining proper moisture balance.²⁷

Prothrombin G20210A mutation

Presentation. Cutaneous presentations of prothrombin gene mutation include tender erythematous and ulcerated papules of the LES, ankle edema, LV, and AB.^{28,29} Cutaneous findings seen with the prothrombin G20210A mutation can mimic chronic LE venous insufficiency, atherosclerotic peripheral arterial disease, inflammatory vasculitides, or pyoderma gangrenosum.²⁹

Laboratory tests. A PCR-based assay is used to determine the presence of this specific mutation at nucleotide position 2010 in the prothrombin gene. In addition to testing for this mutation, a hypercoagulation panel should be performed (Table II). An ultrasound to rule out a DVT should also be included in the work-up if warranted.

Treatment. Long-term anticoagulation with warfarin as described above may be indicated in patients who have early or recurrent thrombosis. Skin ulcerations are managed according to the general principles of wound care as described above. A few studies have reported resolution of skin lesions with enoxaparin.^{28,30}

Antithrombin III deficiency

Presentation. Cutaneous manifestations are uncommon. Recurrent venous or arterial thromboses at an early age may be signs of antithrombin III deficiency (ATIID).³¹ Neonatal purpura fulminans associated with hereditary ATIID has been described.³²

Laboratory tests. An antithrombin (AT) functional assay should be performed if the diagnosis is suspected. An abnormal test result should be repeated at least once, and testing relatives should be considered.³³ Heparin and vitamin K should be discontinued for at least 1 week before repeat testing, because levels will be falsely lower and higher, respectively.³³ All potential causes of

Table II. Hypercoagulation panel

Laboratory evaluation	Key points in interpretation
PT and PTT	Warfarin and other oral vitamin K antagonists and liver disease will significantly prolong the PT. Prolonged PTT could point to antiphospholipid syndrome
Protein C activity	Protein C levels are reduced when patients are taking warfarin
Protein S activity	Acquired causes should be excluded before performing this test. Parents should be screened when questioning a neonate's status. Do not test in acute settings
Homocysteine level	In individuals with an elevated level, it is important to exclude deficiencies in folate or vitamin B12. An abnormal result should be confirmed on a repeat sample. <i>MTHFR</i> mutations can be assayed. Results typically are reported as negative or positive and, if positive, the report will name the mutation(s) present. Often, an interpretation of the results is also provided
Factor V Leiden	
Antiphospholipid antibody panel (ie, anticardiolipin IgG and IgM, lupus anticoagulant, and β 2-glycoprotein-1)	There are no reference ranges for a genetic test: the mutation is either present or absent If any of these are positive, the same test should be repeated in 12 weeks (see Table IV)
Cryoglobulin	If results are negative but suspicion is high, make sure the laboratory stored the blood sample at the correct temperature
Cryofibrinogen	If results are negative but suspicion is high, make sure the laboratory stored the blood sample at the correct temperature
Antithrombin III	This is a genetic test; the results are either positive or negative
Prothrombin G20210A	Normal, heterozygous prothrombin [PT] G20210A, homozygous PT G20210A

IgG, Immunoglobulin G; *IgM*, immunoglobulin M; *MTHFR*, methylenetetrahydrofolate reductase; *PT*, prothrombin time; *PTT*, partial thromboplastin time.

acquired ATIID should be excluded before diagnosing inherited ATIID.³⁴

Treatment. In the absence of a history of thrombosis, long-term anticoagulation is not routinely recommended. Because 42% of episodes of DVT in individuals with ATIID occur in the setting of transient risk factors, such as surgery, diligent DVT prophylaxis in at-risk patients is important, including longer postoperative DVT prophylaxis in individuals with ATIID.³⁵ When prophylaxis cannot be administered before surgery, it is reasonable to administer AT concentrates to a goal activated partial thromboplastin time (aPTT) of 1.5 to 2.^{34,36} Long-term anticoagulant therapy with warfarin may be indicated in the setting of recurrent thromboembolic events.³⁶

Protein C deficiency

Presentation. Heterozygous protein C deficiency is an autosomal dominant condition that has been shown to be associated with DVT and superficial phlebitis later in life. Homozygous protein C deficiency is a rare but life-threatening bleeding disorder that can present in the immediate neonatal period with purpura fulminans that is usually fatal.^{31,37,38} Patients with protein C deficiency may also present clinically with IV.^{1,39,40} Acquired protein C deficiency may present as calciphylaxis,

with skin findings mimicking warfarin-induced skin necrosis, as discussed below.^{3,21}

Laboratory tests. The plasma concentration of protein C in a healthy baby is approximately 40 IU/dL and reaches adult levels after adolescence. A normal plasma concentration of protein C in adults is approximately 65 to 135 IU/dL. Protein C deficiency is considered mild at plasma levels of 20 to 65 IU/dL, moderate to severe deficiency at 1 to 20 IU/dL, and severe deficiency at <1 IU/dL or not detectable.⁴¹ Newborns can have protein C levels <10 IU/dL without manifesting either purpura fulminans or disseminated intravascular necrosis. Protein C levels may be determined quantitatively via enzyme-linked immunosorbent assay (ELISA), which only measures the amount of protein C present and not its functional activity. Functional protein C levels are measured via a clot-based aPTT assay, which measures the time to clot formation after addition of a protein C activator. Functional assays are preferred because they can detect both types of protein C deficiency (type I and II).

Treatment. Management of acute purpura fulminans in the neonatal period involves replacement therapy with fresh frozen plasma or protein C concentrate, intensive wound care, and maintenance anticoagulation therapy that includes low molecular weight heparin (LMWH) and warfarin.^{37,38} Adult

patients with purpura fulminans caused by protein C deficiency should be anticoagulated with heparin before the initiation of warfarin.⁴² Clinical improvement of ulcerations has been reported with a combination of pentoxifylline, aspirin, and dipyridamole.⁴⁰ Oral dapsone reportedly improved skin lesions in 1 case of LV caused by protein C deficiency.³⁹ Management of calciphylaxis caused by protein C deficiency with LMWH and tissue plasminogen activator showed success in case reports.^{3,21} Before elective surgery, patients with protein C deficiency should have adequate anticoagulant prophylaxis to decrease the risk of VTE. When excessive bleeding is anticipated (eg, neurosurgery) and when anticoagulation cannot be safely used, then protein C concentrate can be administered.⁴³

Protein S deficiency

Presentation. Like protein C deficiency, homozygous protein S deficiency is associated with purpura fulminans in neonates.^{37,44,45} Heterozygous protein S deficiency has been associated with Sneddon syndrome and warfarin-induced skin necrosis.⁴⁶⁻⁴⁸ Protein S levels can also be low because of chronic kidney and liver disease, vitamin K deficiency, and disseminated intravascular coagulation.^{21,49} Postinfectious purpura fulminans with acquired protein S deficiency after varicella has been described.^{42,50-53} Patients with protein S deficiency may also present clinically with livedoid vasculopathy.¹

Laboratory tests. The reference range for protein S in men is >73 U/dL and in women is >63 U/dL. Protein S levels do not reach adult values until approximately 6 months of age. Assays for protein S are functional or immunologic. Functional assays (aPTT-based functional protein S assay) measure only free protein S. Immunologic assays (ELISA) measure both free and bound protein S.⁵⁴ Functional assay is again the preferred method of testing.

Treatment. Management of neonatal purpura fulminans involves replacement of protein S with fresh frozen plasma because no protein S concentrate exists.⁴² Additional management is as described for protein C deficiency.

Hyperhomocysteinemia

Presentation. Many case reports have documented elevated homocysteine levels in patients presenting with LV in addition to pale or pink skin, a malar rash, and fine hair.⁵⁵⁻⁵⁷ Hyperhomocysteinemia (HHS) has also been identified as an independent risk factor for psoriasis and mixed cryoglobulinemia.^{58,59}

Laboratory tests. Normal homocysteine levels are <11 μmol/L. Intermediate levels are 11 to

14 μmol/L, high levels are 15 to 29 μmol/L, and very high levels are >29 μmol/L.⁶⁰ HHS can be diagnosed by high-performance liquid chromatography methods or fluorescence polarization immunoassays.^{54,61} In patients with unexpected thrombotic disease, homocysteine levels should be checked as part of the hypercoagulable work-up.⁶² If a patient has elevated homocysteine levels, methylenetetrahydrofolate reductase mutation testing may be ordered.

Treatment. B₆, B₁₂, and folate have been shown to effectively decrease homocysteine levels and attenuate thrombin levels.^{56,63} When LV is present, clopidogrel in addition to vitamin B supplementation may be indicated to achieve resolution of the skin lesions.⁵⁵ Smoking cessation is imperative to normalizing homocysteine levels and resolving skin lesions.

Sickle cell disease

Presentation. Sickle cell disease (SCD) is an autosomal recessive hereditary hemoglobinopathy. Complications of SCD include acute pain episodes, increased rates of vasoocclusive crises, such as stroke, and pregnancy complications. VTE is a common complication of SCD.^{64,65} Patients with SCD typically present to the dermatologist with painful leg ulcers with an AB-like appearance with pain out of proportion compared to the clinical presentation.²⁴ Skin ulcers occur in areas with little subcutaneous fat, thin skin, and decreased blood flow (eg, the anterior aspect of the tibia, dorsal surfaces of the feet, Achilles tendon, or ankles).⁶⁴ Patients start presenting with ulcerations around 20 years of age, and men are more likely to develop ulcers than women.⁶⁶ The ulcers in SCD resemble venous and arterial ulcers but involves deeper tissue.^{24,64}

Laboratory tests. The diagnosis of hemoglobin type is by high-performance liquid chromatography and the sickle test.⁶⁷ When a patient with sickle cell anemia presents with ulceration, a complete blood cell count, renal function tests, urinalysis, liver enzymes, D-dimer, folate, iron, vitamin B₁₂, and homocysteine levels (see above) should be evaluated.⁶⁴ Biopsy specimens obtained of the ulcer are usually nonspecific; sickled erythrocytes are occasionally present in dermal blood vessels.⁶⁴

Treatment. Therapy for ulcers in patients with SCD should focus on prevention (eg, avoiding trauma, treating venous or arterial disease), wound management, and the treatment of secondary infection. Ulcers in SCD often are resistant to treatment. There is report of a combined split-thickness autologous skin graft with hyperbaric oxygen and blood transfusion as successful in

healing a chronic ulcer on the leg caused by sickle cell anemia.²⁴ Pentoxifylline has been reported to be helpful in the treatment of sickle cell ulcers.⁶⁸ The role of hydroxyurea in the treatment of sickle leg ulcers is unclear; however, the weight of evidence suggests that hydroxyurea does not cause, prevent, or speed healing of these ulcers in patients with SCD.⁶⁹ Pain management is also important, and referral to a pain specialist may be necessary.

ACQUIRED HYPERCOAGULABLE STATES

Key points

- The use of anticoagulants can lead to a hypercoagulable state, resulting in skin necrosis
- Retiform purpura is an important physical examination finding in microvascular occlusion syndromes

Warfarin-induced skin necrosis

Skin necrosis usually occurs 3 to 5 days after initiating warfarin therapy with a large loading dose or without concomitant heparin. Skin necrosis affects areas of the body with high fat content and decreased blood supply, such as the breasts, buttocks, abdomen, thighs, and calves. The first signs are pain and purpura that then progress to full-thickness skin necrosis. Warfarin necrosis can also precipitate calciphylaxis. In order to prevent this from occurring, anticoagulation with heparin should be initiated for 4 to 5 days before starting warfarin.⁷⁰ Treatment of warfarin-induced skin necrosis includes discontinuing warfarin, anticoagulation with heparin, and the administration of vitamin K or fresh frozen plasma to reverse the warfarin effect. Local wound care is crucial; depending on the extent of necrosis, surgical debridement and even amputation may be needed.³

Heparin-induced thrombocytopenia

Heparin-induced thrombocytopenia (HIT) is an adverse drug reaction characterized by thrombocytopenia and an increased risk of venous or arterial thrombosis. Skin necrosis is the common clinical sign of this entity. There have been reports of skin necrosis caused by HIT without a drop in platelet count. Treatment of HIT involves the cessation of heparin and initiation of another form of anticoagulant, such as lepirudin, argatroban, or rivaroxaban. Good local wound care and other surgical interventions may be necessary depending on the extent of necrosis. A clinical scoring system has been devised to identify patients with HIT (Table III).⁷¹

Antiphospholipid syndrome

The lupus anticoagulant, anticardiolipin, and anti-β2-glycoprotein-I antibodies have been associated with HSs.³⁶ Physical examination findings include LV and skin ulcers.^{31,72} Patients are often misdiagnosed as having pyoderma gangrenosum and are treated unsuccessfully with antiinflammatory and immunosuppressive agents.⁷³ The international consensus statement defines clinical and laboratory criteria for antiphospholipid syndrome (Table IV).^{74,75} After any single episode of arterial or venous thrombosis, treatment with warfarin is recommended with a goal INR of 2 to 3; treatment duration is controversial.⁷⁶

Thrombotic thrombocytopenia purpura

Thrombotic thrombocytopenia purpura (TTP) can be inherited, acquired, or idiopathic. TTP presents as a pentad of fever, hemolytic anemia, thrombocytopenia, renal failure, and neurologic symptoms. Cutaneous manifestations include petechial and purpuric lesions.^{3,77} Cases of suspected TTP can be confirmed by anti-ADAMTS13 antibodies, low platelets, increased bilirubin, increase lactate dehydrogenase, and a negative Coombs test. Successful treatment of TTP includes plasmapheresis and rituximab.⁷⁸

Cryoglobulinemia and cryofibrinogenemia

Clinical signs of cryoglobulinemia and cryofibrinogenemia include cold intolerance, Raynaud phenomenon, purpura, LR, ulcerations, gangrene, and necrosis resulting from thrombosis.²⁰ When testing for cryoglobulins in serum, the blood sample needs to be collected and kept at 37°C before a determination can be made. If the temperature of the serum falls before clot formation, paraproteins will precipitate out, leading to a false-negative test result. In the testing process, the serum is observed at 4°C for formation of cryoprecipitate. Patients that are concomitantly hepatitis C-positive may see improvement in cryoglobulinemia when treated with interferon-alfa and ribavirin.²⁷ However, patients can flare when interferon-alfa therapy is initiated. Testing for cryofibrinogens is as described for cryoglobulins above, except testing is performed on plasma. Treatment options for primary cryofibrinogenemia include stanazolol, prednisone, plasmapheresis, low-dose warfarin, and avoiding cold exposure.⁷²

In conclusion, the morbidity and mortality related to HSs is significant. Many forms of HS can be inherited, but acquired forms also exist. Adults in HSs commonly present with LV, which includes LR, ulcer formation, edema, and AB scars. In neonates,

Table III. Four Ts scoring system for heparin-induced thrombocytopenia*

	2 points awarded	1 point awarded	0 points awarded
Thrombocytopenia	Platelet count fall >50% and platelet nadir ≥20	Platelet count 30-50% or platelet nadir 10-19	Platelet count fall <30% or platelet nadir <10
Timing of platelet count fall	Clear onset days 5-10 or platelet fall ≤1 day (previous heparin exposure within 30 days)	Consistent with days 5-10 fall, but not clear (eg, missing platelet counts); onset after day 10; or fall ≤1 day (previous heparin exposure 30-100 days ago)	Platelet count ≤4 days without recent exposure
Thrombosis or other sequelae	New thrombosis (confirmed), skin necrosis, or acute systemic reaction postintravenous unfractionated heparin bolus	Progressive or recurrent thrombosis, nonnecrotizing (erythematous) skin lesions, or suspected thrombosis (not proven)	None
Other causes of thrombocytopenia	None apparent	Possible	Definite

*Adapted from Cuker et al.⁷¹ The 4Ts score is the sum of the values for each of the 4 categories. Pretest probability score: 6-8 indicates high; 4-5, intermediate; and 0-3, low.⁷¹

Table IV. International consensus statement on preliminary classification criteria for antiphospholipid syndrome^{74,75}

Clinical criteria	Laboratory criteria
Vascular thrombosis: <ul style="list-style-type: none"> • ≥1 clinical episodes of arterial, venous, or small vessel thrombosis, occurring within any tissue or organ • Thrombosis must be confirmed by imaging studies, Doppler ultrasonography, or histopathology, with the exception of superficial venous thrombosis 	Anticardiolipin antibodies: <ul style="list-style-type: none"> • Anticardiolipin IgG or IgM isotype in serum or plasma present in medium or high titer (>40 IgG phospholipid units [GPL]/mL or IgM phospholipid units [MPL]/mL or >99th percentile)
Complications of pregnancy: <ul style="list-style-type: none"> • ≥1 unexplained deaths of morphologically normal fetuses at or after the 10th week of gestation • ≥1 premature births of morphologically normal neonates at or before the 34th week of gestation because of severe preeclampsia or eclampsia, or severe placental insufficiency • ≥3 unexplained consecutive spontaneous abortions before the 10th week of gestation with maternal anatomic or hormonal abnormalities and paternal and maternal chromosomal causes excluded 	β2-glycoprotein I-dependent anticardiolipin antibodies: <ul style="list-style-type: none"> • Anti-β2-glycoprotein-1 antibody of IgG or IgM isotype in serum or plasma (in titer >99th percentile), present on ≥2 occasions at least 12 weeks apart
Lupus anticoagulant antibodies: <ul style="list-style-type: none"> • Lupus anticoagulant antibodies detected in the plasma on ≥2 occasions at least 12 weeks apart detected in the following steps: <ul style="list-style-type: none"> ○ Prolonged phospholipid-dependent coagulation shown on a screening test ○ Failure to correct the prolonged coagulation time on the screening test by mixing with normal platelet-poor plasma ○ Shortening or correction of the prolonged coagulation time on the screening test by the addition of excess phospholipid ○ Exclusion of other coagulopathies 	

Note that antiphospholipid antibody syndrome is considered to be present if ≥1 of the clinical criteria and 1 of the laboratory criteria are met.

IgG, Immunoglobulin G; IgM, immunoglobulin M.

purpura fulminans is a major clinical manifestation. Prompt diagnosis is imperative. Treatment is directed based on the inciting factor in addition to anticoagulation. Local wound care is imperative in the management of these patients.

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Immediate skin responses to laser and light treatments

Warning endpoints: How to avoid side effects

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Learning objectives

After completing this learning activity, participants should be able to recognize warning endpoints for different laser applications; detail the laser tissue interaction underlying these responses; and select the appropriate endpoints to optimize safety.

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Lasers are versatile, commonly used treatment tools in dermatology. While it is tempting to follow manufacturer's guidelines or other "recipes" for laser treatment, this approach alone can be a recipe for disaster. Specific and immediate skin responses or endpoints exist and are clinically useful because they correlate with underlying mechanisms that are either desirable (ie, therapeutic), undesirable (ie, warning signs of injury or side effects), or incidental. The observation of clinical endpoints is a safe and reliable guide for appropriate treatment. This article presents the warning endpoints during specific dermatologic laser treatments, and the accompanying article presents the therapeutic endpoints, their underlying mechanisms, and the utility of these endpoints. (J Am Acad Dermatol 2016;74:807-19.)

Key words: adverse effects; endpoint; laser; light; skin; warning.

INTRODUCTION

Key points

- **Immediate or short-term tissue reactions, called endpoints, can provide a reliable indicator of desired treatment response or of unwanted tissue injury**

Abbreviations used:

IPL:	intense pulsed light
MTZ:	microthermal zone
Nd:YAG:	neodymium-doped yttrium aluminum garnet
RF:	radiofrequency
SP:	selective photothermolysis

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- **The specific endpoints vary with the type of laser, with proper use of the laser, and with the histologic target(s) involved**
- **Observation of clinical endpoints is crucial for the adjustment of laser parameters during treatment, both to increase efficacy and to avoid side effects**

Lasers and other energy sources are frequently used in dermatology to treat vascular lesions, hypertrichosis, tattoos, various pigmented lesions, scars, photoaging, and skin laxity (Table I). Of all surgical tools, lasers are both the most precise and the most selective. For many applications, there are specific “target” structures or distinct patterns of intended skin injury that achieve the therapeutic response without causing significant collateral injury or scarring. Different anatomic, physical, and physiologic mechanisms are involved in these various applications. As a result, specific immediate and early skin responses or “endpoints” are seen during various laser treatments that correlate with therapeutic outcomes. Other early responses are harbingers of unwanted injury or phenomena that lead to side effects.

We present the clinically useful early response endpoints and their mechanisms that arise during treatment with laser and other energy-based devices in dermatology. Knowledge of specific desired (ie, therapeutic) and undesired (ie, warning) endpoints is key for the proper clinical use of lasers in dermatology. The mechanisms underlying these early response endpoints are also fundamental to understanding laser–tissue interactions. There are 2 articles in this series; the current article presents the warning endpoints, following an overview of lasers, other energy sources, and their tissue interactions and laser safety. The accompanying article presents the specific therapeutic endpoints that are correlated with providing effective treatment.

LASER–TISSUE INTERACTIONS

Key points

- **Selective photothermolysis depends on the preferential absorption of light by the histologic target or chromophore**
- **The laser–tissue reaction in the histologic target produces a specific endpoint in the skin**
- **Nonselective devices produce nonspecific endpoints**

Light, radiofrequency, microwave, ultrasonography, plasma, and other sources that transfer energy into the skin produce their various effects based on the location, amount, and rate of energy absorption

inside the tissue. The absorbed energy is converted to heat, mechanical motion, or chemical reactions. Most laser- and other energy–based treatments in dermatology work by creating heat within tissue at specific target locations or in specific patterns.

When using light sources, basic parameters that describe the dosimetry of treatment must be understood. These include wavelength of light (nm), pulse duration (in seconds), frequency of pulse delivery (Hertz [Hz]), energy (Joule [J]), fluence (the incident energy per unit area, J/cm^2), power (watts [W], the rate of energy delivery), power density or irradiance (the rate of incident energy delivery per unit area, W/cm^2) and exposure spot size (cm). For fractional lasers, the area density (ie, the fraction of skin treated, expressed as %) and pulse energy (ie, J per pulse, corresponding to depth of treatment) are also important.⁸⁴

Many of the lasers used in dermatology affect specific light-absorbing “targets” (eg, blood vessels, pigmented cells, hair follicles, or tattoo ink) based on the process of selective photothermolysis (SP).^{1,85} SP depends on the preferential absorption of light by the targets, provided by light-absorbing molecules called chromophores. For example, blood vessels are treated using hemoglobin as the target chromophores; melanin is the target chromophore for the treatment of hair and for various pigmented lesions; and tattoo inks or exogenous pigments are the chromophores for tattoo and traumatic tattoo removal. Flashlamp sources (intense pulsed light [IPL]) mimic lasers to some extent, using broad spectrum light through cutoff filters to target chromophores. By choosing different wavelengths of light, different chromophores are affected. IPL sources are generally less selective than lasers and may be associated with a greater number of side effects.⁸⁶

For SP, a brief pulse of light is used to limit damage to the tissue surrounding the targets. By delivering the energy in a pulse, the light-absorbing targets become hot before much heat can diffuse into the surrounding tissue. This produces a specific reaction in the target chromophore and in the skin called an endpoint. The pulse duration is chosen to be about equal or somewhat less than the time needed for a target to cool, called the thermal relaxation time. Smaller targets cool faster and need shorter pulse durations for SP. Dermatologic lasers for SP span a wide range of pulse durations. For example, a tattoo ink particle ($\sim 0.05\text{--}1\ \mu m$) cools in <1 microsecond; nanosecond and picoseconds laser pulses are therefore used for tattoo removal. In contrast, a terminal hair follicle ($\sim 75\text{--}200\ \mu m$) takes several milliseconds to cool, such that 1- to 100-millisecond laser or IPL pulses are typically used for permanent hair

Table I. Devices and potential applications (including off-label)

Devices	Applications
Pulsed dye laser ¹⁻⁵	Vascular lesions—telangiectasia, port wine stain, hemangioma, angioma, and venous lake; lentigines; keratosis pilaris; photoaging; poikiloderma; pyogenic granuloma; sebaceous hyperplasia; scars (red); stria (red); and verruca
KTP laser ⁶⁻⁹	Similar to pulsed dye laser, for KTP lasers with similar pulse durations
Alexandrite, long pulsed ¹⁰⁻¹⁶	Hair removal; vascular lesions—hypertrophic port wine stains and lentigines; and benign melanocytic nevi, if appropriate
Q-switched (alexandrite, ruby, Nd:YAG, and frequency doubled Nd:YAG) and picosecond lasers (alexandrite, Nd:YAG, frequency doubled Nd:YAG) ¹⁷⁻²⁴	Pigmented lesions—lentigines, nevus of Ota, café au lait macules, some nevi; tattoos; drug-induced pigmentation (eg, minocycline and amiodarone); melasma (low fluence)
810-nm diode ^{15,16,25-27}	Hair removal; venous lakes; veins; and venous malformations
1064-nm Nd:YAG, long pulsed ²⁸⁻³¹	Hair removal; veins; photoaging; and laxity
Nonablative, nonfractional mid-infrared (1320-1550 nm) ³²⁻⁴⁵	Acne; scars; rhinophyma; hidradenitis suppurativa; and photoaging
Intense pulsed light ⁴⁶⁻⁵¹	Acne; lentigines; hair removal; photoaging; poikiloderma; vascular lesions—telangiectasia, leg veins, and port wine stains
Ablative resurfacing (eg, erbium and CO ₂ lasers) ⁵²	Photoaging; scars; actinic keratoses and cheilitis; seborrheic keratoses; adnexal tumors; rhinophyma; and verruca
Nonablative fractional (wavelengths: 1320, 1440, 1540, 1550, 1410, and 1927 nm) ⁵³⁻⁶³	Scars; photoaging; lentigines; rhytides; poikiloderma; melasma; minocycline-induced hyperpigmentation; residual hemangioma; telangiectatic matting; granuloma annulare; milia; striae; and postinflammatory hyperpigmentation
Ablative fractional (wavelengths: 2790, 2940, and 10600 nm) ⁶⁴⁻⁷¹	Scars; striae; photoaging; laxity; lentigines; rhytides; morphea; drug delivery; anetoderma; and residual hemangioma
Radiofrequency ⁷²⁻⁷⁶	Laxity; rhytides; and cellulite/body contouring
Ultrasonography ⁷⁷⁻⁸³	Laxity; noninvasive fat reduction

KTP, Potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet.

reduction. A millisecond is 1 million times longer than a nanosecond. The wide range of pulse duration correlates with different damage mechanisms and with different corresponding clinical endpoints. Because IPLs emit broad spectrum light in a range of wavelengths, endpoints can be less specific.

Nonselective treatment devices emit energy that is absorbed by water. Because water is present throughout the skin, these wavelengths are not selectively absorbed by specific targets in the skin. There are endpoints associated with these devices, but they are, in general, nonspecific. These include infrared, ablative, and nonablative lasers emitting at wavelengths absorbed by water, various electrosurgical devices, radiofrequency, and focused

ultrasonography. Nonselective treatment devices heat tissue with a depth or pattern that depends on where the energy is delivered.

Ablative treatments remove tissue by vaporizing it. For example, laser skin resurfacing is a classic technique that ablates a thin layer of epidermis and superficial dermis, using CO₂ or erbium lasers.^{52,87} These lasers emit at wavelengths that are strongly absorbed by water.⁸⁸ For laser skin resurfacing, the laser energy is delivered uniformly at the skin surface, and immediate response endpoints are used to verify treatment depth.

Nonablative treatments are those that heat but do not vaporize tissue. The immediate response endpoints for these devices typically relate to thermal coagulation of tissue. Lasers for nonablative

treatments, including fractional nonablative lasers, emit at infrared wavelengths that are weakly or moderately absorbed by water. The nonablative treatment devices in dermatology also include radiofrequency and ultrasonography, which can produce thermal coagulation of tissue deep in the dermis or subcutaneous fat.^{72,73} Focused ultrasonographic energy is able to create a pattern of small zones of thermal injury deep inside soft tissue, near a focal point.^{77,78}

Fractional laser treatments⁵³ use ablative or nonablative lasers that are delivered in differing patterns to produce different clinical results. The laser energy is delivered as an array of small beams, creating a pattern of up to 1000 small wounds per square centimeter of skin called microthermal zones (MTZs). A fraction ($\leq 50\%$) of the skin can be injured, but healing is rapid because each MTZ is surrounded by unexposed, intact tissue. Nonablative fractional lasers produce columns of thermal injury that extend up to about 2 mm deep.⁵³ Ablative fractional lasers vaporize an array of small (0.1-0.3 mm in diameter) vertical channels into the skin that can extend up to 3 mm deep.⁸⁹ Energy delivered per MTZ controls the depth of treatment while the number of MTZ per unit area of skin controls the treatment fraction or the fraction of the area treated.

The laser-tissue interaction between a target chromophore (or histologic target) and a light source elicits a reproducible clinical response. Some clinical responses are suggestive of a therapeutic treatment that will result in removal or partial removal of the intended target. Other clinical responses are warning signs of excess damage to the skin that may result in a scar or other adverse event.

LASER SAFETY

Key points

- Lasers and light sources pose serious hazards
- Lasers and intense pulsed lights can result in blindness and irreversible eye damage—never fire a laser without eye protection and fire precautions in place
- Always place laser and light devices in standby mode before removing goggles
- Always replace goggles before firing a laser

Laser and IPL devices pose serious and potent hazards, especially for eye injury. There are physical hazards, such as fire and electrocution, eye and skin hazards, and biologic hazards, such as plume inhalation of infectious pathogens.⁹⁰ Any individual working with these devices should receive comprehensive safety training. The Laser Institute of

America releases an annual Laser Safety Guide.⁹¹ All operators should have eye protection, fire precautions, and fume extraction. It is the responsibility of the operator to protect the patient and everyone present in the treatment room.

The eye is particularly susceptible to irreversible damage.⁹² Eye damage and blindness can result with even a nanosecond of laser exposure. Retinas, corneas, and lenses are all susceptible.

The endpoints described in these papers are often best seen in visible light without laser goggles. It is paramount that the laser should be placed in the “standby” mode when the endpoint is evaluated without goggles and that laser goggles are replaced before firing the laser.

The warning endpoints

Heat produces a wide range of tissue responses depending on the location, temperature, duration, and rate of heating. Well below the boiling point of water, heat can destroy the structure of macromolecules including enzymes, structural proteins, membranes, DNA, and RNA. At nonlethal temperatures above about 42°C, cells go into “heat shock,” a survival response that potently inhibits normal metabolism and partially blocks apoptosis. Heat shock is a clinically invisible cellular response. From about 50°C to 100°C, most proteins denature and then coagulate (stick to one another), killing cells and causing some visible changes. Protein denaturation is a rate-dependent process that depends on both temperature and time. As such, skin cells can withstand high temperatures for short periods of time (eg, 100°C for a few thousandths of a second) but are killed at the modest temperature of 55°C in a few seconds.^{93,94} There is little difference among cutaneous cell types in their tolerance for thermal injury.^{95,96}

Look for the Nikolsky sign

Key points

- Warning endpoints are skin responses seen immediately or soon after laser irradiation, suggestive of tissue injury
- The Nikolsky sign is an indication of epidermal necrosis, corresponding to loss of dermoepidermal adhesion.
- The Nikolsky sign can be desirable in specific situations

Keratinocyte necrosis is manifested by a positive Nikolsky sign appearing within 5 minutes. When lateral pressure is gently applied with the clinician's finger, the epidermis separates from its underlying dermis.⁹⁷ In this setting, the Nikolsky sign (Figs 1 and 2; Table II) is caused by loss of the actively

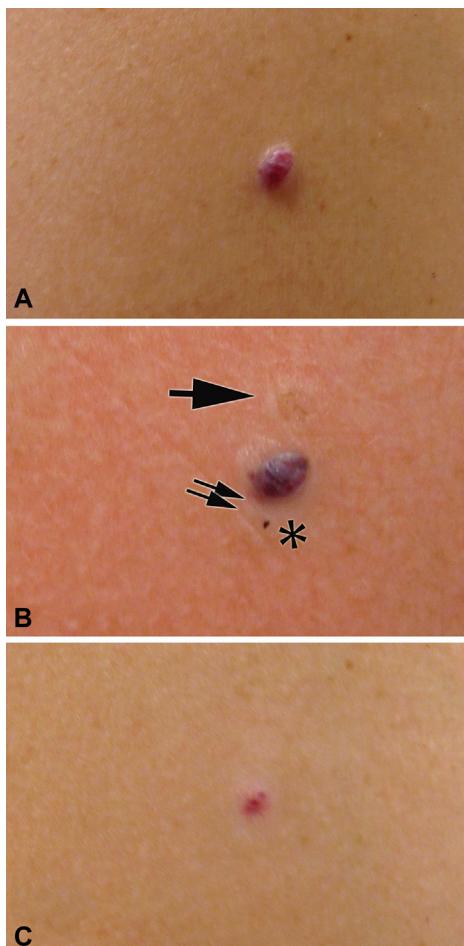


Fig 1. Angioma before (**A**), immediately after (**B**), and 8 weeks after (**C**) treatment with an 810-nm diode laser. There was inadequate compression of the sapphire tip. Note the deep blue color of the angioma that was cooled appropriately. In the areas that were not cooled, there is the Nikolsky sign (*arrow*); dermal whitening and a subtle elevation of the skin (*double arrow*); and charring of the skin (*asterisk*). **C**, Hypopigmentation is evident at 8 weeks posttreatment. This hypopigmentation has persisted 1.5 years after treatment.

maintained adhesion between keratinocytes and dermis. This endpoint is a warning that the epidermis is necrotic and that an open wound is likely to follow with blistering, erosion, or ulceration, along with an increased risk of infection, pigmentary changes, or scarring.

One should look for the Nikolsky sign especially when the risk of unwanted epidermal necrosis is high or if the patient reports strong pain during treatment. Typical situations include treatments of tanned or pigmented skin with any visible or near-infrared laser or flash lamps (IPLs); the use of high fluences or energy settings with any nonablative device; inadvertent pulse stacking (rapidly repeating exposure of a skin site); and a failure to adequately



Fig 2. Superficial erosion of the lip after unintended bulk heating during treatment with a nonablative fractional laser (1540 nm). This photograph was taken 20 minutes posttreatment. The patient washed her face and removed the epidermis in the process, eliciting a positive Nikolsky sign.

cool the skin during treatment. Signs of a skin burn can be difficult to assess because after laser/IPL treatment, the entire field is usually erythematous and edematous. The Nikolsky sign can be present without any other detectable sign of a first- or second-degree burn. Checking for the Nikolsky sign about 5 minutes after a test spot exposure is strongly recommended in these settings.

The Nikolsky sign can be a desired therapeutic endpoint. After the first pass of laser resurfacing or during treatment of congenital melanocytic nevi using the Kono technique,¹⁰³⁻¹⁰⁵ the Nikolsky sign is often present.¹⁰⁶ Gently removing the epidermis with a sterile gauze pad is performed in these procedures to allow for deeper penetration of a second laser pass (Fig 3). The risk of side effects and scarring in these procedures is strongly related to clinical experience. Otherwise, there is no clinical setting for which the Nikolsky sign is a desired therapeutic endpoint during laser treatment.

Skin cooling: Too little, or too much?

Key points

- Second- and third-degree and “stamping” burns correspond to injury because of the failure or misuse of skin-contact window cooling or the use of an incorrect device
- Spotty or crescent-shaped burns or erythema can indicate inadequate or misaligned skin cooling or poor application technique

Actively cooling the skin during laser, IPL, or other energy-based treatments is useful to protect the pigmented epidermis, to reduce pain, and to decrease the risk of skin burns. Skin cooling is accomplished by applying a cold external medium, which can be solid (as with cold windows in some

Table II. Warning endpoints*

Warning endpoint	Description
Nikolsky sign (Figs 1 and 2)	Epidermal separation upon lateral pressure, indicating loss of adhesion between epidermis and dermis because of epidermal necrosis
Second- and third-degree burns (Figs 4 and 5)	Pain, erythema, edema, blistering, and erosion
Stamping epidermal burn (Fig 6)	Epidermal injury caused by the presence of tissue or hair residue on a skin contact window
Crescent moon—shaped injuries (Fig 7)	Epidermal injury caused by cryogen/laser misalignment
Pucker sign (Fig 8)	Immediate skin shrinkage caused by thermal injury of the dermis
Charring (Figs 1 and 9)	Black or brown carbon on the skin caused by tissue carbonization
Chrysiasis ^{98,99} (Fig 10)	Immediate, blue-grey discoloration caused by a Q-switched laser effect on gold particles in the skin
Immediate tattoo darkening ^{100,101}	Immediate dark discoloration caused by laser treatment of ferric oxide or titanium dioxide
Metallic-gray blanching ¹⁰² (Fig 11)	Dermal blood and protein denaturation

*Level IV evidence.

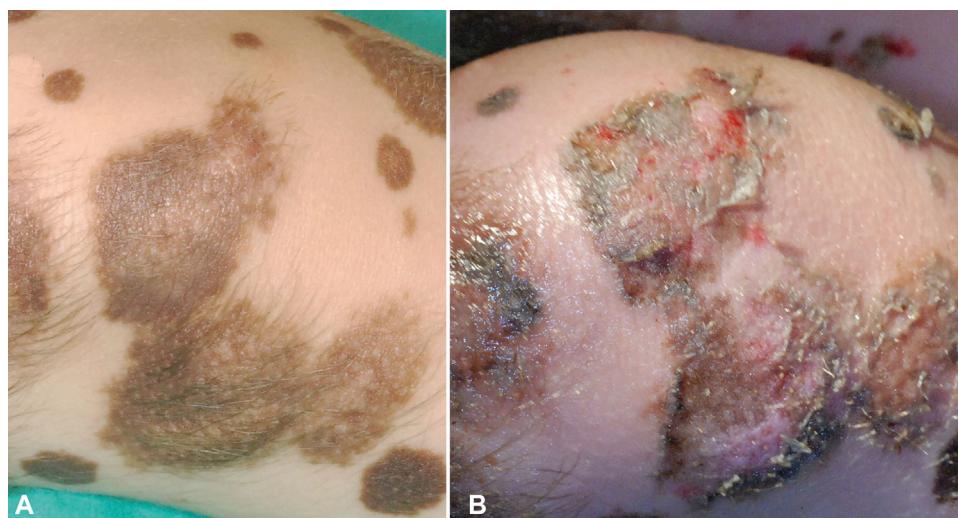


Fig 3. **A**, Congenital nevus treated with a long pulse plus short pulse approach⁹³ before treatment on the left knee. **B**, The Nikolsky sign was induced after 3 milliseconds of exposure to a 755-nm alexandrite laser. Gentle removal of the epidermis was performed with sterile wet gauze in preparation for the second laser irradiation with a Q-switched 1064-nm laser.

IPL and laser delivery handpieces), liquid (as with cryogen spray cooling) or gas (as with forced cold air). When operating properly, skin cooling reduces the risk of side effects and allows the use of higher treatment fluence. However, injury can also occur by misuse or malfunction of skin cooling methods.^{98,107,108} The skin can be injured by either too little cooling or by freezing from too much cooling. Freezing the skin is easily observed as a frosty-white color change.

With cold window devices, poor contact with the skin is an operator-dependent problem that can cause skin burns immediately after exposure (Fig 1).

This can occur with diode lasers, IPLs, and radiofrequency (RF) or ultrasonographic treatments. Deeply penetrating monopolar RF or ultrasonographic treatments can result in fat damage with dimpling of the overlying skin. The warning endpoints of second- and third-degree burns are as follows: severe pain, intense erythema, local edema, blistering, epidermal splatter (ie, pieces of epidermis detach from skin and attach to the laser handpiece window), erosion, or ulceration (Figs 4–6). These iatrogenic burns may heal with erosion/ulceration, crusting, pigmentary changes, secondary infection, and scarring.



Fig 4. A second-degree burn with blistering after the use of a 755-nm alexandrite laser for the treatment of a deep, unresponsive port wine stain.

Inappropriate use of cold window devices can pose additional risks. During laser/IPL hair removal, when a piece of charred hair adheres to a contact window device, energy is strongly absorbed by the charred tissue with each laser pulse. This can cause a “stamping” burn pattern with each subsequent pulse (Fig 6). This potential adverse effect can be simply avoided by cleaning the window both before and during treatment.

Some laser devices incorporate “dynamic” cryogen spray cooling, which coats the skin surface with a spurt of very cold (approximately -50°C) fluorocarbon liquid just before or just after the laser pulse is delivered. Cryogen spray cooling is available on some pulsed dye lasers, alexandrite, and neodymium-doped yttrium aluminum garnet (Nd:YAG) lasers. When used properly, cryogen spray cooling is extremely helpful in protecting the pigmented epidermis from laser-induced injury and reducing the risk of blisters, pain, and swelling. However, excessive cryogen spray duration (eg, >100 ms) can freeze the skin, particularly if used in combination with other cooling devices, such as cold air.

The warning endpoint consists of a bright white frosting that persists for several seconds (Fig 7). Misalignment between the cryogen spray and laser beam can also cause arcuate or crescent “moon-shaped” patterns of skin injury. Even if the device is properly aligned, moon-shaped injury can occur if the laser handpiece is not held perpendicular to the skin surface. Sometimes it is unclear whether such arcuate injuries were caused by a cryogen injury or a laser burn injury, but both mechanisms can be prevented by proper alignment and positioning of the laser/cryogen handpiece and close observation of treatment endpoints.



Fig 5. A second-degree burn showing the value of cooling to protect pigmented epidermis. The arrow points to a second-degree burn of porcine skin after failure of skin cooling. The double arrow points to an area treated with the same laser and proper epidermal cooling. There are no signs of a burn.

Skin shrinkage is a sign of dermal injury

Key points

- Skin contraction and the “pucker sign” are indications of a dermal burn, corresponding to thermal denaturation of collagen
- Immediate shrinkage of the dermis can cause the skin to become slightly elevated and firm
- Unintended ablation is an indication of thermal burn
- “Charring” indicates a severe burn, corresponding to carbonization of tissue

Type I collagen is the most abundant protein in the dermis. When heated above about 70°C , type I collagen undergoes a helix-to-coil conformational change, leading to immediate skin shrinkage.⁹⁴ This endpoint is always an indication of significant thermal injury to the dermis. For some applications, a moderate amount of immediate shrinkage is a useful therapeutic endpoint (eg, during the final pass of ablative laser resurfacing or during high-density ablative fractional laser treatments). However, in any application where dermal injury is unwanted, immediate shrinkage is an ominous warning endpoint that should lead the clinician to stop treatment and reassess the situation. For example, immediate skin shrinkage should not be seen during nonablative laser treatments or during any application of selective photothermolysis (eg, vascular lesions, pigmented lesions, tattoo removal, or hair removal). This warning sign is not limited to laser treatments and can also occur during IPL, RF, ultrasonographic, or plasma exposure.

Shrinkage can be observed in several ways. First, the skin will visibly contract during laser exposure. However, it can be difficult to see this endpoint through protective laser goggles and impossible to see when using an occlusive handpiece. The “pucker sign” is another, more reliable indicator of



Fig 6. **A**, Stamping burn pattern after the use of an 800-nm diode laser with a dirty cold contact window. **B**, Hair char is present on the cold window.



Fig 7. Freezing of the skin from excessive cryogen spray cooling. In this case, 100-ms of cryogen spray was applied both before and after delivery of an 8-mm diameter alexandrite laser pulse. A halo of skin surrounding the laser exposure is frozen. When the frost persists for more than a few seconds, freeze injury is likely to occur. The cryogen spray duration should be reduced.

skin shrinkage—the skin surface lines assume a radial pattern pointing to the center of the exposure from a laser or other device (Fig 8). A more subtle sign of immediate shrinkage of the dermis is slight elevation of the skin and firmness to palpation (Fig 1).

One unfortunately common and preventable cause of scarring is the use of any IPL device for treatment of tattoos. The pulse duration of all IPL devices is too long for selective photothermolysis of tattoos.⁹⁹ The puckered lip sign is sometimes seen during this inappropriate use of an IPL.

Controlled tissue ablation is the goal during vaporization of verrucae and other lesions, during laser resurfacing, and during ablative fractional resurfacing; however, ablation during other types of procedures is a sign of excessive tissue injury. During any nonablative procedure, ablation of the skin should not be seen. In addition to signaling a thermal burn, tissue ablation poses a biohazard, and protective measures should be taken whenever tissue ablation is seen. For example, during Q-switched



Fig 8. “Pucker sign,” a radial pattern of superficial skin lines caused by immediate skin shrinkage. The pucker sign is illustrated by this test exposure using a defocused CO₂ laser. Immediate shrinkage is a warning endpoint of significant thermal injury to the dermis. Some immediate shrinkage is normally seen during ablative laser resurfacing, but in most other settings this is an ominous endpoint.

laser treatment of tattoos, pieces of live tissue can be explosively expelled from the skin, flying rapidly toward the treating physician. Depending on country of origin, people with tattoos are more likely to have viral hepatitis or HIV.^{100,101,109} If the patient harbors viral hepatitis or HIV, health care personnel can be directly exposed to ablated, infectious tissue fragments. In addition, laser plumes from tissue ablation or from partial combustion of hair during laser or IPL hair removal can be irritating or toxic.⁹⁸

Charring is another warning endpoint. When energy continues to be applied to tissue after most of its water is removed, partial combustion occurs, and the tissue surface becomes charred. Charring consists of a thin layer of black or dark brown carbon adhered to the tissue surface (Figs 1 and 9). Skin charring is generally associated with excessive thermal damage (eg, caused by the improper use or



Fig 9. Charring of the skin appears as black or dark brown material adherent to the tissue surface (arrow). The material is carbon released by partial combustion. During ablative laser procedures, charring of the skin is a sign of excessive thermal injury.



Fig 10. Laser-induced chrysiasis is a blue-grey discoloration of the skin caused by Q-switched laser exposure. It occurs in patients with a history of gold intake. Chrysiasis is permanent and difficult to treat.

malfuction of a resurfacing laser [conventional or fractional] or plasma device).

Other specific warning endpoints

Key points

- **Immediate blue-grey darkening during Q-switched laser treatment indicates chrysiasis, a potentially permanent side effect in patients with a history of gold intake**
- **Immediate tattoo darkening during Q-switched laser treatment indicates a chemical alteration of tattoo inks that may not be removed with subsequent treatments**
- **Immediate metallic-gray blanching of skin is a sign of dermal overheating**

Some warning endpoints are highly specific. Q-switched laser treatment of a patient who has been treated at any time with gold often causes an



Fig 11. Metallic gray blanching of the skin after the use of a high-fluence 755-nm alexandrite laser for the treatment of port wine stain.

immediate, permanent blue-grey discoloration of skin. This is laser-induced chrysiasis,¹¹⁰ a specific warning endpoint created by the interaction of the Q-switched laser with gold deposits that remain in the skin for a lifetime. The situation can be avoided by obtaining a history of gold therapy before any Q-switched laser treatment. However, some patients may not recall taking gold decades ago or may not recognize gold exposure unless made aware that “aurothiomalate” is a gold-based medication used for arthritis, for example. Particularly in a patient with a history of rheumatoid arthritis, a good habit is to deliver 1 test pulse in a hidden, non–sun exposed skin site, such as the inner upper arm, then look for a blue-grey skin discoloration without laser goggles (Fig 10). In some cases, laser-induced chrysiasis can be improved by subsequent treatment with long-pulse lasers or IPLs.¹⁰²

Tattoo ink darkening is another warning endpoint that is specific to Q-switched laser treatment.^{111,112} Tattoo inks that contain red iron oxide or white titanium dioxide generally turn black or dark gray immediately upon exposure to a Q-switched laser. This darkening is thought to be caused by the chemical reduction of ferric oxide to ferrous oxide. Tattoo ink darkening is irreversible, but the darkened tattoo ink can sometimes be removed by subsequent laser treatments.¹¹³ The most common setting for laser-induced tattoo ink darkening is during treatment of cosmetic tattoos used as permanent lip liner or for eyebrows. Common colors include flesh, pink, rose, or reddish colors.¹¹⁴

Finally, when using vascular-targeting lasers, the immediate metallic-gray blanching of the vascular lesion

can indicate nonspecific dermal injury and the need to immediately reduce the treatment fluence or provide better skin cooling (Fig 11). This is especially important when using near-infrared lasers, such as alexandrite, Nd:YAG, or diode lasers for vascular destruction.¹⁰ Overheating the vessels will cause heat propagation beyond the target vessels, damaging the surrounding dermis. Clinically, the injury progresses with necrosis, ulceration, crusting, and possibly scarring.

In conclusion, specific and observable responses during laser or IPL treatments can be indicators of therapeutic benefit or a warning of unwanted skin injury or other unwanted events. These endpoints are more useful than a list of “dosimetry” settings for various devices and indications. It is the physician’s responsibility to recommend and use appropriate devices for treatment of a given problem and individual patient; to take a relevant history; to prepare the patient and the skin before treatment; to use skillful application techniques; and to adjust the treatment device for proper parameters. Appropriate wavelength choice for each chromophore, dosimetry, pulse duration, and skin cooling are crucial for success.

The Nikolsky sign, second- and third-degree burn signs, stamping epidermal burns, immediate skin shrinkage, and charring of the skin are warning endpoints related to the use of an inappropriate fluence, an incorrect device, the wrong pulse duration, or the failure of cooling devices. Q-switched lasers have specific warning signs, such as chrysiasis and immediate tattoo ink darkening. Overheating of vessels can be observed as an immediate metallic-gray blanching of the skin. Skin response endpoints should be used in lieu of a “cookbook” approach because variations in skin pigmentation and sensitivity are common, and because the output or calibration accuracy of devices vary between manufacturers and usually change over time and after routine maintenance. Careful observation of warning endpoints after a test spot treatment and during treatment can decrease the risk of severe side effects.

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Immediate skin responses to laser and light treatments

Therapeutic endpoints: How to obtain efficacy

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Learning objectives

After completing this learning activity, participants should be recognize therapeutic endpoints for different laser applications; detail the laser tissue interaction underlying these responses; and optimize treatments based on the choice of the appropriate endpoints.

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Clinical endpoints are immediate or early tissue reactions that occur during laser treatment. They can guide the laser surgeon in delivering safe and effective laser treatment. Some endpoints act as warning signs of injury to the skin; others can indicate a therapeutic response. The first article in this series reviewed undesirable and warning endpoints, and this article focuses on desirable and therapeutic endpoints and their underlying mechanisms in laser surgery. We will also review treatments without clinical endpoints. (*J Am Acad Dermatol* 2016;74:821-33.)

Key words: endpoint; immediate skin responses; laser; light; skin; therapeutic.

INTRODUCTION

Key points

- Immediate or short-term tissue reactions, called endpoints, can provide a reliable indication of treatment response
- Different endpoints correlate with different underlying mechanisms
- Some—but not all—lasers elicit specific therapeutic endpoints

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Abbreviations used:

μm:	micrometer
IH:	infantile hemangioma
IPL:	intense pulsed light
KTP:	potassium titanyl phosphate
Nd:YAG:	neodymium-doped yttrium aluminum garnet
PDL:	pulsed dye laser
RF:	radiofrequency

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Table I. Therapeutic endpoints*

Target	Device	Endpoint
Port wine stain	PDL, KTP, Nd:YAG, and alexandrite	Purpura [†]
Hemangioma	PDL	Subtle, transient purpura
Telangiectasia, veins	PDL, KTP, Nd:YAG, and IPL	Vessel disappearance or transient vessel graying
Hair removal	Alexandrite, ruby, IPL, Nd:YAG, and diode	Perifollicular edema with or without erythema [‡]
Lentigines	Q-switched lasers (eg, alexandrite, ruby, and Nd:YAG)	Immediate whitening
	Long pulsed lasers (eg, PDL and 532-nm) or IPL	Subtle darkening; ash gray appearance (PDL)
Nevus of Ota	Q-switched and picosecond lasers	Immediate dermal whitening
Tattoo	Q-switched and picosecond lasers	Immediate dermal whitening

IPL, Intense pulsed light; KTP, potassium titanyl phosphate; Nd:YAG, neodymium-doped yttrium aluminum garnet; PDL, pulsed dye laser.

*Level IV evidence.

[†]Purpura may not be possible at safe fluences with devices with longer pulse widths.

[‡]May be difficult to appreciate in patients with dark skin.

How does one know that a therapeutic “dose” of energy is being delivered? Lasers usually elicit immediate or short-term responses of the skin. These laser–tissue reactions are “endpoints,” and they can provide a reliable indicator of treatment response. The clinical endpoint depends on both the laser or light treatment used and the target of the laser.

Specific clinical endpoints are seen when a laser or light source has a specific histologic target. These light-absorbing targets or chromophores include blood vessels, pigmented cells, hair follicles, and tattoo ink. Based on the theory of selective photothermolysis, chromophores can be targeted with minimal damage to the surrounding skin using pulses of light from lasers or flashlamps (IPL)—that is, pulses of light from lasers or flash lamps. Selective photothermolysis treatments for hair removal, tattoo removal, and vascular and pigmented lesions have distinct endpoints.

In addition, the clinical endpoint depends on the mechanism of interaction between a histologic target and a specific laser. The photothermal, photomechanical, and photochemical effects of light pulses and the nature of the target impact the endpoint. Long-pulsed and Q-switched lasers of the same wavelength have different endpoints for the same lesion.

For ablative and nonablative lasers that use water as a chromophore, the response endpoints are less specific. These treatments generally heat the epidermis or dermis in various patterns to create either thermal coagulation/protein denaturation or ablation (ie, tissue vaporization).

Although therapeutic endpoints do not guarantee a clinical response, specific therapeutic endpoints, with a few important exceptions, are a useful tool for setting proper laser or IPL dosimetry (Table I). Careful observation of therapeutic endpoints (in the absence of a warning endpoint) is more reliable

than using “recommended” or “preset” laser settings as the primary guide during treatment. This is because the endpoints relate directly to an intended laser–tissue interaction regardless of the variations between individual patients and individual laser devices.

The previous article in this series reviewed laser–tissue interactions and “warning endpoints”—that is, endpoints suggestive of tissue injury—and also discussed laser safety, which is crucial to the use of these endpoints. The clinical endpoints associated with vascular lesions, hair removal, tattoo removal, and pigmented lesion removal will be reviewed in this article. Fractionated and mid-infrared lasers that target water as the chromophore will also be reviewed.

THERAPEUTIC ENDPOINTS

Key points

- Endpoints depend on multiple factors, including laser wavelength, pulse width, target, fluence, and skin type
- If an endpoint is not achieved, increasing the fluence may not be the solution—always look carefully for warning endpoints
- Achieving a therapeutic endpoint does not guarantee the absence of side effects

Our collective clinical observations of therapeutic endpoints appear below. The endpoint depends on a variety of factors, including wavelength, target, pulse width, and fluence. In general, the safest and most efficacious approach is to use the lowest fluence possible to obtain the therapeutic endpoint in the absence of a warning endpoint. If an endpoint is not achieved, increasing the fluence may not be the solution. Adjustment of other features may be necessary, such as wavelength, pulse width, or evaluation of the health status of the patient.

The medical provider must take a detailed history that includes a patient's medical history, medications, allergies, and sun exposure history.¹ Endpoints may appear different in patients with skin of color. The physician must consider skin type and skin condition in the treatment area. In addition, the presence of a therapeutic endpoint does not guarantee the absence of side effects. If a tan patient is treated or an inappropriate laser is chosen for the patient's skin type, an adverse event can result despite the presence of a therapeutic endpoint. Decreasing the risk of complications depends on both the choice of the right treatment for the right patient and the treatment itself. Treatment risks should always be reviewed.

VASCULAR LESIONS

Key points

- **The endpoint for vascular lesions depends on the type of lesion**
- **Immediate purpura is the endpoint of choice for port wine stains treated with vascular-specific lasers**
- **Immediate vessel disappearance or vessel darkening is the therapeutic endpoint for telangiectasias treated with vascular-specific lasers or intense pulsed light therapies**

The applications for vascular treatment lasers and some IPLs are broad and include port wine stains (PWSs) and other microvascular malformations, hemangiomas, telangiectasia and erythematous rosacea, spider and cherry angiomas, verrucae, erythematous scars, and poikiloderma. The use of lasers to treat vascular lesions relies on the theory of selective photothermolysis.² The basis of this theory is that pulses of light at a specific wavelength are preferentially absorbed by oxyhemoglobin or deoxyhemoglobin. The sources used for vascular lesions in dermatology emit pulses of green (532-nm potassium titanyl phosphate [KTP] lasers), yellow (585–600 nm pulsed dye lasers [PDLs]), or near-infrared laser (755–1064 nm alexandrite, diode, or neodymium-doped yttrium aluminum garnet [Nd:YAG]). At the correct wavelength, fluence, spot size, and pulse duration, these lasers can target vascular lesions.

For a given laser treatment to be selective, a combination of correct wavelength, correct pulse duration, and correct fluence must be chosen. In general, optimal pulse duration is about equal to the thermal relaxation time of the target vessels. Thermal relaxation time in seconds is approximately equal to the square of the vessel diameter in millimeters. For very small vessels—such as those of pediatric PWSs

and infantile hemangioma—short pulse durations (0.4 to ~3 ms) are necessary to match the thermal relaxation time of microvessels.^{3–5} For larger vessels, such as adult facial telangiectasia, longer pulses that better match the thermal relaxation time of these larger vessels (6 to ~50 ms) are used. The immediate therapeutic endpoints are different for short versus long pulses and for small versus large target vessels.

Port wine stains (capillary malformation)

PDLs entered dermatology specifically for the treatment of pediatric PWSs, and are still the most specific and widely used sources for treatment of children and adults with PWSs and other microvascular malformations. Purpura is the therapeutic endpoint of the PDL in this setting. KTP lasers and IPLs have also been used to treat PWSs.^{6–8} The endpoint for these devices can differ depending on the wavelength and pulse duration. A longer pulse width at the same wavelength and same fluence may not produce purpura. Purpura, the endpoint of choice with a PDL for pediatric PWSs, may not be possible at safe fluences with devices emitting pulses longer than ~3 ms.

In general, longer wavelengths in the visible and near infrared range are capable of deeper treatment. The alexandrite laser, which at 755 nm in the near infrared spectrum penetrates far deeper into the skin than green or yellow light, is useful for treatment of adults with hypertrophic PWSs⁹ and somewhat useful for children with “resistant” PWSs that show rapid refilling after compression with an examining finger (indicating high blood flow). The Nd:YAG laser (1064 nm) is able to treat adult PWSs throughout the entire dermal thickness and into subcutaneous fat, but is more treacherous to use than PDLs because of the need for much higher fluences,¹⁰ the formation of methemoglobin during the laser pulse,¹¹ and a tendency to damage arterioles more than the target vessels, which are primarily venules.¹²

The appropriate therapeutic endpoint for PDL treatment of a PWS is purpura limited to the laser exposure spot size^{7,13} (Figs 1 and 2). The threshold fluence for this response varies with pulse duration and wavelength of the laser and with the hemoglobin level of the patient. When hemoglobin is thermally denatured, its iron atom is oxidized, forming methemoglobin, a dark pigment that absorbs red light. As a consequence, blood turns from bright red to a dark grey or black color. Within a few minutes, the damaged walls of the PWS vessels leak, causing petechial hemorrhages that change the color to a dark red-purple and create purpura.¹⁴ Intensity of purpura has been correlated with clearance of PWSs in patients treated with the PDL,⁷ although



Fig 1. **A**, Before pulsed dye laser treatment. **B**, Immediate purpura is the appropriate endpoint for treatment of port wine stains. This baby was treated with pulsed dye laser (6.5 J/cm^2 fluence, 0.45 ms pulse duration, 12 mm spot size, DCD 30/20).

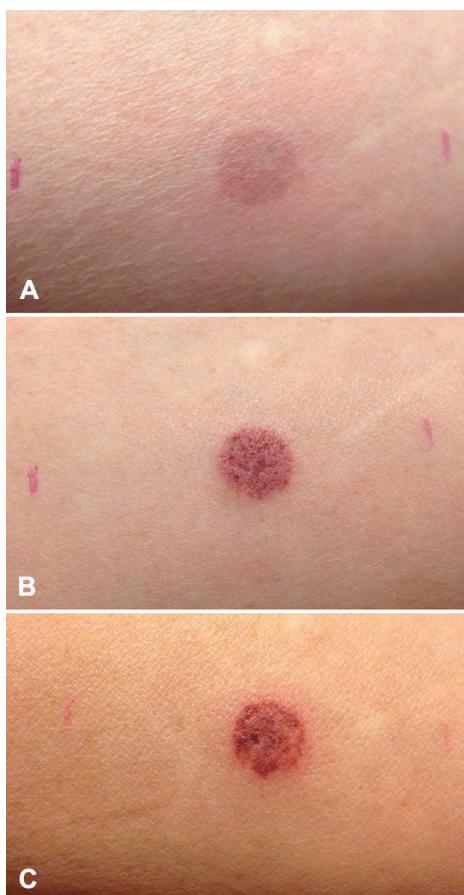


Fig 2. **A**, Purpura after pulsed dye laser immediately after treatment. **B**, One minute posttreatment. **C**, Twenty-four hours posttreatment.

treating beyond the purpuric threshold increases the risk of perivascular damage.¹⁵ Nevertheless, regions of persistent perfusion exist despite clinically visible purpura, and this endpoint does not indicate a complete clinical response.¹⁶

If the immediate purpuric endpoint is not achieved with typical PDL settings (7–10 mm spot size, 0.4–3 ms, 6–9 J/cm^2), the laser calibration should be checked and the exposure repeated. If purpura is still not achieved, the patient may be anemic or the lesion may not be a PWS. For example, a mixed lymphatic-vascular microvascular malformation with low hemoglobin content can masquerade as a PWS. Additional evaluation of the patient is needed—not cranking up the laser fluence. Having blood-filled target vessels is also needed for successful PWS treatment. For patients under general anesthesia, changes in vasomotor tone can collapse the small target venules. When this occurs and the expected therapeutic endpoint of purpura is not seen, continuous positive airway pressure can be used to increase central venous pressure, filling the target vessels and restoring the desired endpoint. The immediate purpuric response of PWSs is also useful for ensuring that a uniform pattern of pulses has been delivered; an “egg-crate” pattern with large skip areas between adjacent pulses is not adequate. The darkest purpura after PDL treatment occurs 1 or 2 days after treatment, at which time histopathology reveals a leukocytoclastic vasculitis.¹⁷ Purpura fades gradually over the next 7 to 10 days.

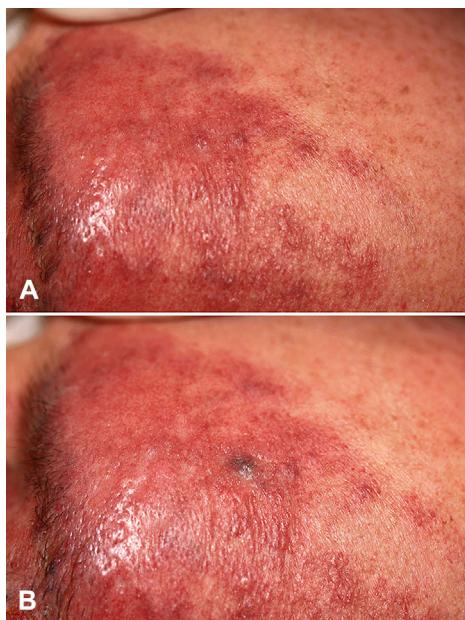


Fig 3. **A**, Port wine stain of the forehead before treatment. **B**, Purple blue endpoint of the alexandrite laser after 1 pulse in the center of the lesion.

With the more deeply penetrating wavelengths from alexandrite or Nd:YAG lasers, the appropriate therapeutic endpoint when treating PWSs is subtly different and important to minimize the risk of skin burns. Unlike the PDL, these deeply penetrating near-infrared lasers should be delivered at or barely above the lowest fluence that causes purpura. In addition, the purpura threshold fluence with these lasers can vary widely between patients compared with that for PDLs¹⁰ and should be determined individually.⁹ The purpura of these lasers is purple blue in color (Fig 3).

Infantile hemangiomas

Unlike vascular malformations, the goal of treating infantile hemangiomas (IHs) with a laser is not to destroy target vessels, but to initiate a biologic response cascade that initiates regression of the treated tissue. Mechanisms involved in this response are unknown. PDL treatment triggers the early clearance of proliferating or stable IHs,¹⁸⁻²³ and may be useful for rapid resolution of ulcerated painful hemangiomas.²⁴ Aggressive PDL treatment of IH is not necessary and can induce ulceration²⁵ or permanent pigmentation abnormalities, especially if appropriate skin cooling is not used.¹⁹ Short (eg, 0.4-ms) yellow dye laser pulses at a fluence of 4.5 to 7 J/cm² delivered with 20 to 30 ms of cryogen spray cooling and a 7- to 10-mm spot size are typically optimal. In this clinical setting, the appropriate immediate response endpoint is subtle

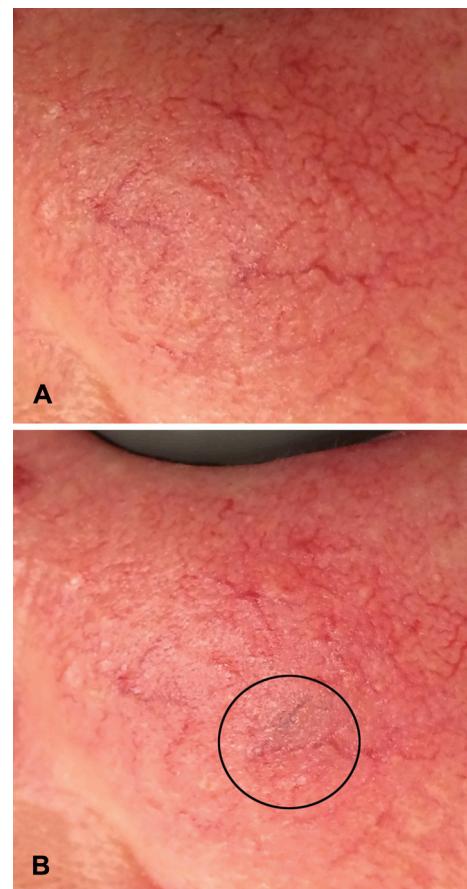


Fig 4. **A**, Telangiectasia before treatment with a pulsed dye laser. **B**, Transient vessel darkening after treatment with a pulsed dye laser (circled).

purpura, which may be transient. Subtle and prompt darkening of the lesion may follow within 1 minute.

The advent of oral and topical beta adrenergic-blocking drugs for the treatment of IH²⁶⁻²⁸ has decreased the need for laser treatment, which is now reserved mainly for poorly responsive or ulcerated lesions or poor tolerance to propranolol.

Telangiectasia

Regardless of cause (eg, rosacea, "spider" angioma, photoaging, CREST syndrome, etc), the 2 useful therapeutic endpoints for laser or IPL treatment of telangiectasia are immediate vessel darkening or immediate vessel disappearance (Fig 4). Purpura is not necessary, and is usually not appreciated by patients with facial telangiectasia.¹⁵ IPL and lasers can be used to treat telangiectasia, including PDL, KTP, and Nd:YAG.²⁹⁻³¹

Compared with PWS treatments, longer pulse durations (typically 10-50 ms) are used for laser or IPL treatment in order to spare small normal vessels from injury and to avoid purpura. These longer pulse

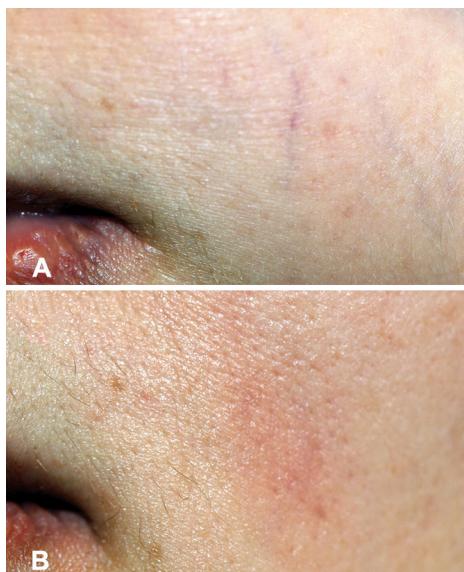


Fig 5. **A**, Facial veins before treatment with an 810-nm diode laser. **B**, Vessel disappearance after treatment with an 810-nm diode laser.

durations better target facial telangiectasia, which typically includes vessels with diameters of 200 to 500 μm .³² Immediate vessel darkening is caused by thermal denaturation of blood with formation of the dark pigment methemoglobin. Immediate vessel disappearance requires somewhat higher fluence than immediate darkening. This therapeutic endpoint is caused by a photothermal effect that results in clearing of blood from the vessel lumen. In some larger vessels, this endpoint results from steam formation in the vessel lumen.¹⁴ The photothermal effects are contraction of the blood plasma caused by thermal coagulation and collagen denaturation in the target vessel wall. This laser–tissue interaction results in vessel shrinkage, causing the lumen of the vessel to empty.

Malformations of large veins, such as venous malformations, are treated using long pulses in combination with appropriate skin cooling with visible lasers, near-infrared lasers, or IPLs. Unwanted normal cutaneous veins or spider veins in fair-skinned individuals—up to ~3 mm in diameter—can be removed using diode (800-nm) or Nd:YAG (1064-nm) pulses in the 20 to 100 ms range^{33,34} (Fig 5). As with small telangiectasias, darkening or immediate disappearance of the target vessels are the therapeutic endpoints. For large vessels, such as cutaneous veins or those of venous malformations treated with these long pulses, vessel disappearance is often associated with a dull “pop” sound, caused by an expanding intravascular steam bubble.

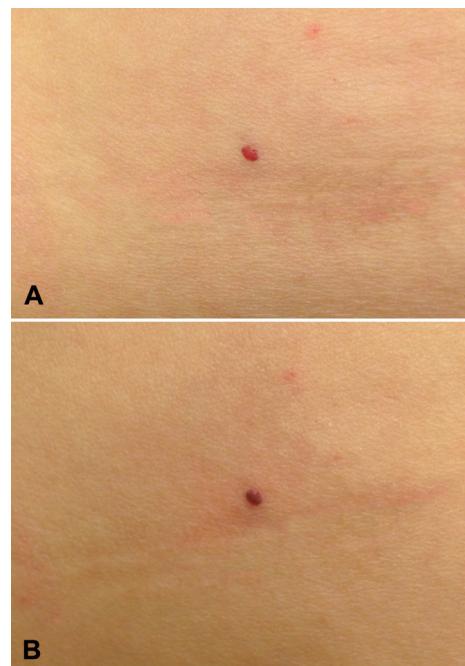


Fig 6. **A**, Cherry angioma before pulsed dye laser therapy. **B**, Purpura with surrounding erythema after pulsed dye laser therapy.

Other vascular lesions

Purpura without petechiae is a useful therapeutic endpoint for the treatment of cherry angiomas. These lesions are typically treated with vascular lasers, such as PDLs or KTPs at short pulse durations. Purpura is indicative of intravascular coagulation, as opposed to hemorrhage of the vessel in this setting (Fig 6).³⁵

Venous lakes respond well to ~800-nm wavelength diode lasers using 30-ms pulse durations.³⁶ Vessel darkening or disappearance is the therapeutic endpoint (Fig 7). As with large vessels and venous malformations, a dull “pop” sound can be heard or kickback of the handpiece can be felt during treatment because of a steam bubble.

HAIR REMOVAL

Key points

- The therapeutic endpoint for hair removal appears after several minutes
- Perifollicular erythema and edema are the most reliable endpoints
- Vaporization or charring of hair may be seen with some lasers, but these are not required for therapeutic response

Hair removal is accomplished at wavelengths absorbed by melanin in the 600 to 1100 nm range, using pulse durations ranging from about 1 to

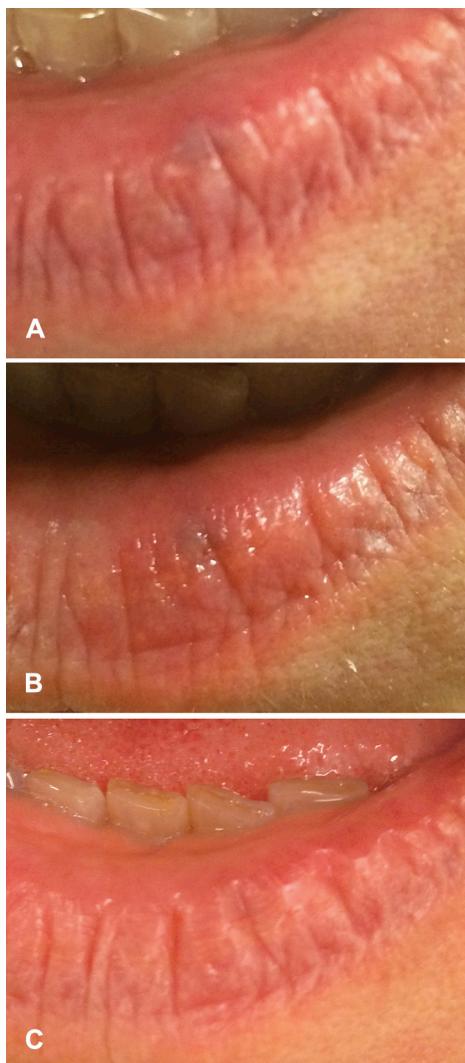


Fig 7. **A**, Venous lake before treatment with an 810-nm diode laser. **B**, Immediate darkening after treatment at 39 J/cm^2 and 30-ms pulse duration through a cold sapphire window with 3 seconds prepulse and postpulse contact cooling. A dull “pop” is heard at the time of laser exposure because of intravascular steam bubbles. **C**, Six weeks posttreatment.

200 ms. Ruby lasers (694-nm), alexandrite lasers (755-nm), diode lasers (810-nm), Nd:YAG lasers (1064-nm), and IPLs are used to photothermally target melanin in the hair follicle. Overall, the goal is to irreversibly damage pigmented hair follicles without significant damage to the overlying pigmented epidermis. Nd:YAG lasers are generally safer for reducing black hair in patients with dark skin. Compared with shorter wavelengths, 1064-nm light is poorly absorbed by melanin and therefore less likely to injure a pigmented epidermis. Skin cooling should be used, especially in pigmented skin. To date, no laser or IPL system is able to remove white hair.



Fig 8. **A**, Leg hair before treatment with a long pulsed 755-nm alexandrite laser with dynamic cryogen cooling, operating at 1.5-ms pulse duration. **B**, After treatment with alexandrite laser. Note the perifollicular erythema and edema, appearing several minutes after laser hair removal treatment. This therapeutic endpoint is seen with other hair removal lasers and intense pulsed light therapies. In this case, some hair shafts were also vaporized, which does not constitute a therapeutic endpoint per se.

Millisecond-domain long pulse durations are required for hair removal. The terminal hair follicle is large ($\sim 75\text{--}200\ \mu\text{m}$) and takes milliseconds to cool. In addition, permanent hair reduction requires destruction of stem cells in the outer root sheath of the follicle, necessitating even longer pulse durations to allow for propagation of heat from the pigmented hair shaft to the nonpigmented stem cells. As a result, 1 to 100 ms laser or IPL pulses are needed for permanent hair reduction. Shorter pulse durations are better for thinner, finer hairs.

The most reliable therapeutic endpoint for permanent laser or IPL hair reduction is perifollicular erythema and edema developing within a few minutes after exposure (Figs 8 and 9). This endpoint corresponds to an eosinophilic inflammatory reaction associated with injury to the hair follicle.³⁷ The degree of perifollicular erythema and edema is associated with a greater perifollicular reaction.³⁸⁻⁴⁰ In patients with darker skin, erythema is sometimes difficult to appreciate. Side-lighting the skin will show perifollicular edematous papules in any skin type.

Although there may be vaporization or charring of the visible hair shafts, there should be no charring, blistering, crusting, or ulceration of the skin. Long pulsed lasers, such as the diode with contact cooling, can char the hair. Care should be taken to remove the char from the window of the laser, or a burn can result (see the first article in this series). Hair removal



Fig 9. Perifollicular erythema and edema after hair removal with the 810-nm diode laser with contact cooling. Note the untreated hairs in between the treated areas. Charring of the hairs is visible and often seen with this laser, but is not a therapeutic endpoint.

lasers with a short pulse duration (eg, 1.5-3 ms alexandrite laser) tend to vaporize the hair shaft. The first laser system approved for hair removal was a Q-switched Nd:YAG laser device delivered after topical application of a carbon suspension.⁴¹ In this case, the pulse duration was so short (~10 ns) that hair shafts were vaporized without sufficient time for heat transfer to viable cells of the hair follicle that surround the shaft.^{37,41,42} This system was not shown to produce permanent hair reduction⁴³ and suggests that immediate vaporization of hair is not a reliable therapeutic endpoint.

PIGMENTED LESIONS

Key points

- **The endpoint depends on the pulse duration of the laser or light source**
- **Q-switched lasers cause immediate whitening**
- **Long pulsed lasers and light sources cause subtle darkening that will take several minutes to appear**

Lentigines

The most selective treatment of benign lentigines uses very short pulses (10-100 ns) in the visible or near-infrared wavelengths (eg, 532-, 694-, or 755-nm Q-switched lasers) operating at typical fluences ranging from 2 to 6 J/cm², respectively. The targeting of pigmented cells with these short pulses is mediated through selective photothermolysis of melanosomes.⁴⁴⁻⁴⁸ The therapeutic endpoint is immediate whitening confined to the pigmented lesion, which corresponds to cavitation and rupture of melanosomes with release of gas bubbles into the tissue^{44,46,49} (Fig 10). The immediate whitening response fades over 3 to 20 minutes as these gas bubbles dissolve. When the Q-switched Nd:YAG (1064-nm) or frequency-doubled Q-switched

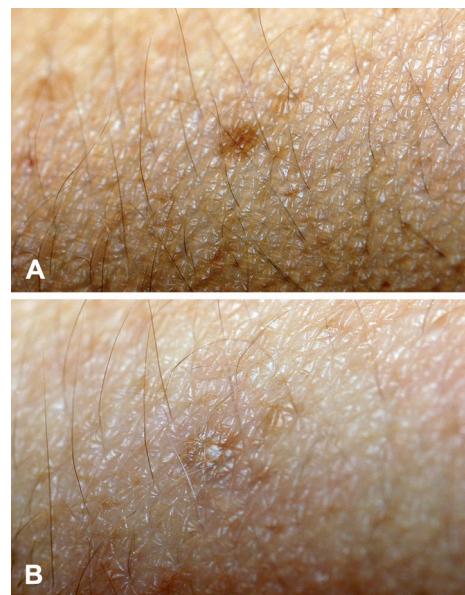


Fig 10. A, Lentigo before exposure with a Q-switched ruby laser. **B,** Immediate whitening after exposure with a Q-switched ruby laser. The response, caused by melanosome rupture, fades over several minutes.

Nd:YAG laser (532-nm) are used for treatment of lentigines, the therapeutic endpoint of immediate whitening is similar, but absorption by hemoglobin at these wavelengths often causes purpura or petechial hemorrhages.⁵⁰

Long (millisecond domain) optical pulses are also appropriate for treatment of lentigines, but the therapeutic endpoint is not immediate whitening. With longer pulses from millisecond lasers or IPLs, subtle darkening of the lentigines without change in the normal surrounding skin is the therapeutic endpoint. This endpoint is sometimes followed by perilesional erythema that appears within several minutes⁵¹⁻⁵⁶ (Fig 11). Histologically, the subtle darkening endpoint corresponds to necrotic pigmented cells in the epidermis.⁵⁷ Patients should be warned that the treated lesions are likely to continue darkening, giving skin a peppered or “dirty” appearance for several days before the lesions are removed by desquamation.

PDL delivered with firm diascopy through a transparent window can also be used to treat lentigines without concomitant damage to blood vessels.⁵⁸ With firm pressure (diascopy), blood is forced from the dermis, temporarily removing hemoglobin and enabling lentigines to be targeted without concomitant vascular injury. PDL causes subtle darkening or an ash-gray color change in the lesion after several minutes. Long pulsed lasers are associated with a lower risk of postinflammatory hyperpigmentation than the use of Q-switched lasers in Asian patients.⁵⁸



Fig 11. **A**, Lentigo on the forehead before intense pulsed light treatment. **B**, Several minutes after intense pulsed light treatment. Note the subtle darkening.

Nevus of Ota

Nevus of Ota is a dermal melanocytosis common among Asian patients that almost always responds well to treatment with Q-switched lasers (eg, ruby, alexandrite, and Nd:YAG).⁵⁹ The appropriate therapeutic endpoint is immediate dermal whitening limited to the lesion and not occurring when adjacent normal skin is exposed.^{44,60} Immediate dermal whitening may be less intense and less crisp than immediate epidermal whitening that, for example, follows treatment of lentigines with a Q-switched laser. Increasing fluence much beyond the threshold for immediate dermal whitening typically does not increase the efficacy of treatment and may cause unwanted epidermal damage. Edema and erythema typically follow immediate whitening. Erythema may be difficult to appreciate in patients with darker skin. Purpura may also be seen incidentally when treating nevus of Ota with a Q-switched Nd:YAG laser. Picosecond lasers can also be used (Fig 12).

TATTOOS

Key points

- The endpoint for tattoo removal is immediate whitening
- This endpoint corresponds to small gas bubbles in the dermis

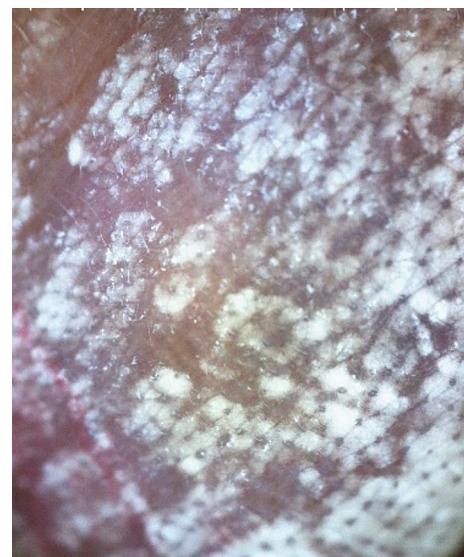


Fig 12. Immediate whitening of a nevus of Ota after treatment with a picosecond laser at 5.26 J/cm^2 , 5 Hertz, and a 2.2-mm spot size.

- Long pulsed lasers or intense pulsed light therapy should not be used for tattoo removal

The appropriate therapeutic endpoint when treating a tattoo with a Q-switched laser or picosecond laser is immediate dermal whitening in the tattooed skin⁶¹⁻⁶⁵ (Fig 13). The treated tattoo may also be immediately raised by about 1 mm because of the volume of small gas bubbles. Whitening corresponds to light scattered by small gas bubbles that form in the dermis and fades gradually as these bubbles dissolve. In this regard, the therapeutic response is similar to that during Q-switched laser treatment of pigmented lesions. Electron microscopy studies show that Q-switched and picosecond laser treatments decrease the size of the tattoo pigment particles and release the pigment particles that are housed in fibroblasts into the extracellular space.^{61,63,66,67} The pigment is then shed in scale crust, removed with an inflammatory response, or repackaged into various dermal cells.^{61,68,69} A recent study suggests that the immediate whitening response interferes to some extent with penetration of light into the tattoo. In one study, a series of laser passes performed with sufficient time for fading of the whitening (about 20 minutes) between passes was found to be more effective than conventional treatment with a single laser pass.⁷⁰ In this case, the therapeutic response of immediate whitening partially interferes with depth of penetration into the dermis.

Tattoos should not be treated with long (millisecond) optical pulses, particularly with IPLs,

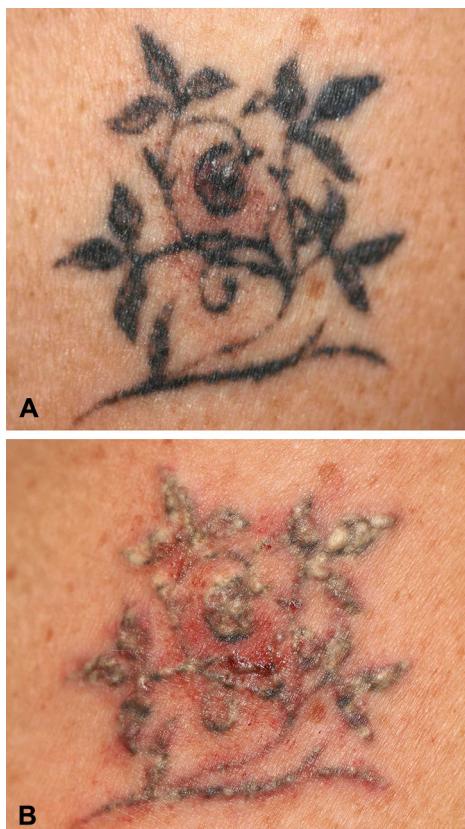


Fig 13. **A**, Tattoo before treatment with a Q-switched ruby laser. **B**, Immediate whitening after treatment with a Q-switched laser. Note that the port wine stain in the center of the tattoo does not have whitening, illustrating the principle of selective photothermolysis.

because of a high risk of scarring.^{71,72} These long pulses greatly exceed the thermal relaxation time for ink particles and the cells that contain ink. As a result, there is heat diffusion to the dermis that results in damage to the normal skin.

LASERS WITHOUT SPECIFIC ENDPOINTS

Key points

- There are no specific therapeutic endpoints for fractionated lasers and nonablative mid infrared lasers
- Small white dots or dark dots that correspond to treated areas may be seen with fractionated lasers
- Any immediate endpoint with nonablative mid infrared lasers suggests dermal necrosis
- Proper dosimetry is crucial to the use of these lasers

Nonablative fractionated lasers

There are multiple nonablative fractional devices that use various wavelengths.^{73,74} Proper dosimetry and application technique are critical in fractional



Fig 14. Small holes are seen immediately after treatment with fractional erbium laser. Each hole is about the size of a terminal hair, surrounded by a thin off-white collar of coagulated epidermis. Tissue fluid or blood usually leaks for several days from these holes.

laser treatment because there is not an easily seen, specific therapeutic endpoint. Attention to cooling and avoidance of pulse stacking is important to avoid burns. If a Nikolsky sign or a pucker sign is seen (covered in the first article in this series), it is likely that a dermal burn has occurred. Treatment with nonablative fractional lasers may or may not cause small white dots that correspond to microthermal zones. Edema and mild erythema can be appreciated a few minutes after treatment. Small dark dots and a darkening of lentigines and pigmented lesions may be noted within minutes to hours, especially after the 1927-nm thulium laser fractional treatment. Histologically, there is thermal damage to the epidermis and dermis, but little inflammation immediately after treatment.⁷³

Ablative fractionated lasers

Ablative fractional lasers produce a pattern of small holes that may be easily seen with magnification but may be barely noticed with the unaided eye (Fig 14). The size of the holes depends on the device. The histologic counterpart to this clinical finding are open channels surrounded by a zone of thermal coagulation.⁷⁵ Bleeding may inform the physician about the relative depth of ablative fractional treatment, but is not a therapeutic endpoint. Bleeding is typically more common with erbium:YAG lasers rather than CO₂ lasers because of less thermal coagulation. Bleeding is influenced by the state of the skin (ie, normal, mature scar, or new scar) and the pulse width of the treatment; longer pulse widths lead to more coagulation and less bleeding.⁷⁶ As the depth of the laser goes beyond the papillary dermis, oozing of edema fluid is typically seen several minutes after treatment.

Nonablative (nonfractional) mid-infrared lasers

Lasers at wavelengths that are moderately absorbed by water are available for the treatment of photoaging or for acne vulgaris. Specifically, a variant of Nd:YAG laser emitting at 1320 nm^{77,78} or semiconductor diode lasers emitting at 1450 to 1550 nm⁷⁹⁻⁸⁶ are delivered through a cold contact window or in combination with cryogen spray cooling. The desired interaction is to create an “upside-down” first-degree skin burn, with nonspecific thermal injury of the superficial and mid-dermis, without injury to the epidermis. These devices are sometimes referred to as subsurfacing lasers.⁷⁷ There is no immediate therapeutic endpoint when using these devices. If the laser fluence is high enough to produce an observable immediate response, that response consists of a raised white papule that corresponds to dermal coagulation and necrosis. These lasers should be used at fluences below that causing any visible immediate response. Subtle erythema develops several minutes after appropriate treatment.

In conclusion, specific and observable responses during various laser or IPL treatments can indicate therapeutic benefit or be a warning of unwanted skin injury or other unwanted events. These endpoints are more useful and flexible than predetermined dosimetry—the “cookbook” approach—for various devices and indications. Unfortunately, the cookbook approach is often used, and even sometimes rigidly taught. It is the physician’s responsibility to recommend and use appropriate devices for treatment of a given problem in an individual patient; to take a relevant history; to evaluate each patient and lesion to be treated; to use skillful application techniques; and to adjust the device parameters to achieve a safe, effective treatment.

Skin response endpoints should be used, because variations in skin pigmentation and sensitivity are common, and because the output or calibration accuracy of devices frequently change over time. Similar devices from different manufacturers or even the same manufacturer might deliver different energies, wavelengths, or pulse durations. Skin cooling systems designed to protect the skin vary and can fail. A good combination of efficacy and safety is obtained by treating at or near the fluence needed to achieve the desired therapeutic endpoint while avoiding warning endpoints. Understanding the basis for therapeutic and warning endpoints and paying attention to these immediate skin responses while providing safe and effective treatments is highly recommended.

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Allergic contact dermatitis

Patient diagnosis and evaluation

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Learning objectives

After completing this learning activity participants should be able to identify patients suspected of allergic contact dermatitis who may benefit from patch testing and describe the appropriate patch testing technique and testing materials in order to fully evaluate patients suspected of allergic contact dermatitis.

Disclosures

Editors

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Allergic contact dermatitis resulting from exposure to a chemical or chemicals is a common diagnosis in the dermatologist's office. We are exposed to hundreds of potential allergens daily. Patch testing is the criterion standard for diagnosing the causative allergens responsible for allergic contact dermatitis. Patch testing beyond standard trays is often needed to fully diagnose patients, but not all dermatology practices have access to this testing procedure or these allergens. In order to adequately evaluate patients, physicians must understand the pathophysiology of the disease process and be well versed in the proper evaluation of patients, indications for patch testing, proper testing procedure, and other diagnostic tools available and be aware of new and emerging allergens. (J Am Acad Dermatol 2016;74:1029-40.)

Key words: allergens; allergic contact dermatitis; atopy patch test; delayed-type hypersensitivity; dermatitis; patch testing.

Contact dermatitis, both irritant and allergic, is a common entity in the dermatologist's office. Contact dermatitis is caused by contact with 1 of the hundreds of chemicals to which individuals are exposed on a daily basis. Management of patients with contact dermatitis can be challenging but rewarding for both patients and physicians alike—most notably when a chemical or chemicals can be identified and removed from the patient's environment resulting in clearing of a dermatitis that may have been present for years.

Abbreviations used:

ACD:	allergic contact dermatitis
AD:	atopic dermatitis
APT:	atopy patch test
LTt:	lymphocyte transformation test
MCI:	methylchloroisothiazolinone
MI:	methylisothiazolinone
NACDG:	North American Contact Dermatitis Group
ROAT:	repeat open application test
SCD:	systemic contact dermatitis
T.R.U.E.:	Thin-layer Rapid Use Epicutaneous

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Persistence, consideration of contact dermatitis as a diagnosis, and a detective-like approach is often needed to identify the causative chemical(s). Allergic contact dermatitis (ACD) is common, but the actual incidence of ACD is difficult to capture because patients often self-diagnose or enter the medical system at various points, such as the emergency room, primary care offices, and urgent care clinics. ACD should be considered in patients with ongoing dermatitis. Identifying the causative allergen(s) is crucial to the resolution of this process. The criterion standard for diagnosing ACD is patch testing; patients suspected of having ACD should undergo this testing to elucidate the allergen(s) responsible for the dermatitis. We present an ACD update herein, including the tools used to evaluate and diagnose patients.

Numerous groups have grown out of the specialty of contact dermatitis. The North American Contact Dermatitis Group (NACDG), founded in 1970, helped arrange the 20-allergen kit sold in the United States after the US Food and Drug Administration (FDA) reclassified allergens in the United States, dramatically changing allergen availability at the time. They continue to publish on allergens in North America. The International Contact Dermatitis Research Group, European Environmental and Contact Dermatitis Research Group, and the European Society of Contact Dermatitis are some of the many international groups dedicated to furthering the professional exchange and knowledge in the field. The American Contact Dermatitis Society is an active group, holding an annual meeting and having >850 members. This group has developed a core allergen series, allergen narratives in both English and Spanish describing >70 allergens to be used as patient education tools, and a database called the Contact Allergen Management Program (CAMP) that provides patients with products that are safe to use given their known allergens.¹

The history of patch testing and contact dermatitis is too rich to be adequately outlined in this review, but several detailed accounts have been published.²⁻⁴

PATHOPHYSIOLOGY: BASIC SCIENCE

ACD is a type IV, delayed-type reaction that is caused by skin contact with allergens that activate antigen-specific T cells in a sensitized individual. The sensitized T cells are primarily T-helper 1 ($T_{H}1$) type. In the sensitization phase, innate immunity is activated through keratinocyte release of interleukin (IL)-1 α , IL-1 β , tumor necrosis factor-alpha, granulocyte-macrophage colony-stimulating factor, and ILs-8 and -18. Langerhans and dermal dendritic cells uptake the allergen and migrate to

the regional lymph nodes to activate antigen-specific T cells (ie, $T_{H}1$, $T_{H}2$, $T_{H}17$, and regulatory T [Treg] cells). These T cells then proliferate and enter the circulation and site of exposure. When reexposed to the allergen, antigen-specific T cells are activated through the release of cytokines and induce an inflammatory process. We now also recognize that patients with atopic dermatitis (AD) have barrier dysfunction that contributes to ACD in that population.⁵

Dermal dendritic cells, as opposed to epidermal Langerhans cells, play an important role in educating naïve T cells in the lymph node to become antigen-specific effector cells during cutaneous sensitization.⁶ The recognition of skin resident T cells has enlightened our understanding of the role of Langerhans cells. Langerhans cells have now been shown to interact with skin resident T cells and generally promote tolerance when encountering antigens by stimulating Treg cells. However, in the presence of pathogens, such as *Candida albicans*, Langerhans cells stimulate T effector memory cells and promote inflammation.⁷

An increased appreciation of epidermal immunology increases our understanding of known therapies and may lead to innovative treatments and diagnostic tests. Systemic corticosteroids were recently shown to encourage Treg cell proliferation in patch test sites of patients with ACD to nickel.⁸ Topical 1,25-dihydroxyvitamin D also induces Treg cells, probably by primarily affecting antigen-presenting cells.⁹

PATCH TESTING

Indication for patch testing

Patch testing is the criterion standard in the diagnosis of ACD. Patch testing attempts to recreate, *in vivo*, an allergic reaction to nonirritating concentrations of an allergen that is suspended in a vehicle. The decision to perform patch testing and which allergens to test depends on many factors.

Some common indications for patch testing include: (1) distributions that are highly suggestive of ACD—for example, ACD of the hands, feet, face, and eyelid, as well as unilateral presentations; (2) a clinical history that is highly suggestive of ACD; (3) high-risk occupations for ACD—for example, health care workers, cosmetologists, and florists, etc; (4) dermatitis of unknown etiology; (5) worsening of a previously stable dermatitis; and (6) dermatitis that is unresponsive to treatment.

Patch testing is also indicated if ACD is thought to develop secondarily in the course of another endogenous inflammatory disease. This typically occurs because of sensitization from topical

Table I. Patch testing chambers

Chamber name	Company	Characteristics
IQ/IQ Ultra	Chemotechnique Diagnostics, distributed by Dormer Labs Inc, Toronto, Ontario	10 square chambers per strip; polyethylene foam chamber; filter paper incorporated into the chamber; each unit has plastic cover for ease of storage
Finn	SmartPractice Finland, Tuusula, Finland	10 round aluminum chambers, 8 mm per strip; separate filter paper
AllergEAZE	SmartPractice Canada, Calgary, Alberta, Canada	10 square, 8-mm chambers; inert acetal copolymer; prefixed filter paper; rounded corners
van der Bend	Van der Bend BV, Brielle, The Netherlands	Chambers can be fixed on tape
Haye's Test	HAL Allergenen Laboratorium BV, Haarlem, The Netherlands	Notches in chambers allow filling without removing the cover
T.R.U.E Test	SmartPractice, Phoenix, AZ	Prefabricated and prepackaged chambers; 3 panels each with 12 allergens

T.R.U.E., Thin-layer Rapid Use Epicutaneous.

Table II. Allergen suppliers

Company	Distributor	Contact information
AllergEAZE	SmartPractice Canada, Calgary, Alberta, Canada	info@allergeaze.com
Chemotechnique Diagnostics	Dormer Laboratories, Inc, Toronto, Ontario, Canada	www.dormer.ca
T.R.U.E Test	SmartPractice, Phoenix, AZ	info@smartpractice.com

T.R.U.E., Thin-layer Rapid Use Epicutaneous.

treatments, either prescribed or over the counter, in the treatment of diseases such as AD and psoriasis.¹⁰

Systemic contact dermatitis (SCD) describes a cutaneous eruption from systemic exposure to an allergen and is another indication for patch testing.¹¹ There are multiple routes of exposure for the elicitation of SCD, including oral, intramuscular, intravenous, transepidermal, and subcutaneous.¹² SCD has a wide spectrum of presentations, including: (1) widespread erythematous papules or dermatitis¹³; (2) deep-seated vesicles of the palms and fingers¹⁴; (3) flexural erythema of the extremities¹⁵; (4) confluent erythema of the anogenital region and intertriginous areas¹⁶; (5) lip and perioral dermatitis¹⁷⁻¹⁹; and (6) periocular swelling or dermatitis.^{19,20}

TESTING PROCEDURE

Supplies

In addition to allergens, other supplies required include tape, a refrigerator for storage of the allergens, chambers, A Wood's lamp, markers, and maps.

Patch tests are used to identify the cause of ACD and aim to reproduce an eczematous reaction to a causative allergen applied to intact skin. Closed patch testing involves the application of allergens under occlusion to the skin of the upper aspect of the back for a period of 2 days. Readings are generally performed at that time, with additional delayed readings.

Allergens are placed in a patch test chamber. The chamber is an inert material applied to a hypoallergenic tape providing excellent occlusion while adhering the test unit to the skin. Each strip contains a separate chamber for an individual allergen. Chambers can be composed of aluminum or plastic and have a diameter ranging from 8 to 10 mm. Petrolatum-based allergens are placed directly into the chamber; liquid-based allergens are placed onto filter paper within the chamber. There are many companies that supply patch testing chambers (Table I). Reinforcement of patch test units with supplemental tape is often recommended. Some of the newer alternatives are water-resistant. More than 4350 chemicals have been identified as contact allergens.²¹ Many cases of ACD are caused by a relatively small number of allergens. Patients are typically tested to a standard or screening series of allergens. In more advanced patch testing centers, specialty series are used that can be directed to specific exposures based on the patient's unique background. In some instances, patients are patch tested to non-commercially available allergens and extreme caution is necessary to avoid severe irritant reactions, false-positive and -negative reactions, and sensitizing to a new allergen. There are references available to help guide the use of non-commercially available allergens.²²

Several companies supply commercially available allergens (Table II).

It is important to preserve the location of allergen placement. Anatomic locator diagrams and digital photography can be used to identify the location of the patches. Fluorescent markers can be used to outline the patch test units and prevent staining of clothing. The use of a Wood's lamp elucidates the otherwise invisible markings.

On hairy areas of the back, it may be necessary to use a clipper to remove excess body hair. In patients with oily skin, it may be necessary to degrease the skin gently with ethanol or other mild solvents before the application of the patch test materials.²³

Allergen selection

Allergen selection is dependent on history, physical examination, and allergen availability. Regional dermatitis, such as localized eyelid or hand dermatitis, might prompt testing to certain allergens. Specific avocations or occupations may lead to targeted allergen testing (ie, the plant tray for a florist or a dental tray for the dental technician). More often than not, a standard series is used as an initial starting point, with other series added as indicated by history, physical examination, and availability. In the United States, there is 1 series approved by the FDA: the Thin-layer Rapid Use Epicutaneous (T.R.U.E.) Test (SmartPractice, Phoenix, AZ). It was initially introduced in 1995 with 23 allergens and 1 control. This easy to use, preimpregnated testing system increased the number of patch tests performed.²⁴ However, many allergens were undetected because of the limited number of allergens.^{25,26} Five additional allergens were added to improve detection rates; in 2012, 7 more allergens were added, bringing the current T.R.U.E. Test to 35 allergens and 1 control, which has improved the detection of allergy. Studies have shown that almost 27% of allergens may still be missed using this series.^{27,28} Allergens that have not been approved by the FDA can be obtained from other sources (**Table II**) and have been shown to perform better, detecting a higher rate of causative allergens. However, even expanded series beyond what is approved by the FDA can fall short, emphasizing the need for a detailed history that can direct expanded allergen selection.^{27,28} Specific categories, such as botanicals, prove particularly difficult to test for because adequate screening series are lacking and the number of allergens is extensive.²⁹ The choice of allergens used in patch testing is in part dependent on the resources in an individual's practice. The T.R.U.E. Test is a good starting point for clinicians who do not routinely perform extensive patch testing. However, ACD and its causative allergens may be missed if expanded testing beyond standard trays are not performed. If expanded testing is not locally

available, referral to a patch test center should be considered, because studies have shown that patch testing is cost effective and has been shown to decrease costs in patients with ACD.³⁰

Patch test reading

All patch test systems are designed to occlude allergens on the patient's skin for 2 days, allowing for adequate penetration of the allergen into the skin. An initial interpretation is performed after patch tests are removed. Adequate time is needed for the cutaneous effects of occlusion, such as transient erythema, to resolve. Supervised removal of the patch tests is necessary to assess the adequacy of occlusion, ensuring that the integrity of the patch test procedure is not compromised. If loose tests are noted, retesting should be considered.

A second or delayed reading should take place 72 to 168 hours after the allergens were initially applied. This reading is critically important to distinguish irritant reactions from true allergic reactions and to identify allergic reactions that do not appear at the time of patch removal.³¹ Depending on the allergen, delayed readings beyond that time may be necessary.³² Examples of allergens that require delayed readings include neomycin, nickel, and topical corticosteroids.³³

Allergens are typically placed on the upper aspect of the back because it is the area most studied for reproducibility in patch testing. When testing only a limited number of allergens, or if all allergens will not fit on the patient's back, it is acceptable to place them on the outer upper arm (ie, for retesting). While it is sometimes necessary to place patches on areas other than the upper back (ie, the arms, legs, and abdomen), these areas are nonstandard placement sites and may be associated with false-negative or -positive reactions.

The accuracy of patch testing patients on systemic immunosuppression has not been well established with large studies. In 1 small prospective study, positive reactions were seen in patients who were taking azathioprine, cyclosporine, methotrexate, mycophenolate mofetil, infliximab, adalimumab, and etanercept.³⁴ In a small, placebo-controlled study, oral prednisone (20 mg/day) was found to suppress the number of positive nickel reactions in patients with known sensitivity to nickel.³⁵ Ideally, patients would no longer be taking immunosuppressive drugs before patch testing, but this is not always possible.

Practical considerations

There are several important items that may affect the choice of patch testing. For example, clinicians should delay patch testing if the patient has a recent

Table III. Classification of patch test readings according to the International Contact Dermatitis Research Group

Reaction	Definition
?+	Doubtful reaction; faint erythema only
1+	Weakly positive reaction; erythema, infiltration, and possible papules
2+	Strongly positive reaction; erythema, infiltration, papules, and vesicles
3+	Extreme positive reaction; intense erythema, infiltration, and coalescing vesicles
-	Negative reaction
IR	Irritant reaction: patterns include follicular, glazed erythema, and ulceration
NT	Not tested

history of sun exposure because of the potential for false-negative reactions.³⁶ Patch testing a patient with widespread dermatitis can result in false-positive reactions. In addition, patients should avoid corticosteroid creams on the test area in the days before testing.

Oral corticosteroid use with prednisolone >10 mg daily or an equivalent is a relative contraindication to testing, because it may suppress positive reactions.³⁵ Positive patch test results can be seen in patients who are taking other immunosuppressive drugs if there is no possibility of stopping them.³⁴ Antihistamines may be continued throughout testing unless one is looking to evaluate for contact urticaria.³⁷ If the patient is pregnant, patch testing should be deferred until after pregnancy, although there is neither strong evidence of any deleterious effects on pregnancy outcomes nor evidence that the immunologic changes of pregnancy affect the accuracy of patch testing.³⁸ Finally, if the patient's skin contains excess sebum or hair, hair removal and gentle degreasing can be performed with ethanol or another mild solvent.

Reading and grading the results of patch testing is somewhat subjective and dependent on descriptive morphology. This creates a large degree of variation in how patch tests are read by different clinicians. There is a range of intensity from mild to severe that includes erythema, edema, vesicles, and bullae. For a reaction to be considered positive, there should be at least some degree of erythematous infiltration or papules. Erythema without any infiltration would be considered a sign of a doubtful or irritant reaction. Unfortunately, there is still a lack of complete consensus on how to grade patch test readings. The clinician generally grades the positive readings from 1+ to 3+³⁹ (Table III).

Potential reasons for false-negative reactions. False-negative reactions can be caused

by: (1) failure to perform a delayed reading; (2) testing to an inappropriately low concentration of allergen; (3) poor patch test placement or loosening of patch tests; and (4) concurrent immunosuppression (eg, sunlight, topical or systemic corticosteroids, and other immunosuppressive drugs).

Potential reasons for false-positive reactions.

False-positive reactions can be caused by: (1) testing with borderline irritants (eg, metals, formaldehyde, and epoxy); (2) testing beyond the irritancy threshold; (3) excited skin syndrome (ie, angry back syndrome); and (4) patients with a background of dermatitis.

Relevance

Once allergens have been identified through patch testing, the relevance of the allergens to the clinical scenario must be determined. Relevance can be past, present, or unknown. An allergen with past relevance is an allergen identified on patch testing and correlating with a past dermatitis. For example, a patient with hand dermatitis, a positive reaction to neomycin, and a history of reactions when using over the counter antibiotics has past relevance. The neomycin is relevant to the history, but not to the current hand dermatitis because the patient has no current exposure to neomycin. Present relevance is what the clinician and patient are searching for through the patch test process. Present relevance is determined when the allergen is identified in the patient's environment and removal of the allergen clears the dermatitis. Unknown relevance is when a patient is found to react to an allergen and no current or past exposure is identified. Certain allergens, such as formaldehyde releasers, when found to be positive, have a high rate of relevance. Other allergens, such as thimerosal, do not often have high relevance to the current dermatitis and as such have been dropped from testing by the NACDG and many patch test centers.^{40,41}

Other diagnostic tests

Patch testing is the criterion standard for diagnosing ACD, but there are problems with this test. Many subjects without clinically problematic dermatitis will have positive patch tests to nickel, cobalt, thimerosal, fragrance, and colophony.⁴² Therefore, a positive patch test does not equate to a diagnosis of ACD. The patch test may indicate past relevance or the patient may have another diagnosis unrelated to the positive patch test. Other diagnostic tests include repeat open application tests (ROATs), lymphocyte transformation tests (LTTs), and atopy patch tests (APTs).

Repeat open application tests. ROATs can be used to verify that an antigen causing a positive patch test will lead to dermatitis when present at usage concentrations. A ROAT may need to be conducted for several weeks.⁴³ A ROAT is performed by applying approximately 0.1 mL of the test substance (ie, leave-on personal care products) twice daily to an area approximately 5 × 5 cm, such as the antecubital area and upper arm.⁴⁴ While a positive response usually occurs in 2 to 4 days, it is advisable to extend the applications beyond 7 days to capture late-appearing reactions. Scented cosmetics, including deodorants and moisturizers, can require considerably more time to cause reactions—up to 28 days or 56 applications. Ideally, it is recommended to perform the ROAT at 3 distinct sites because of the variability in reactivity on different areas of the skin. Such sites include the antecubital fossa, back skin, and the outer aspect of the upper arm.⁴⁵ ROATs with deodorants may be performed in the axilla under conditions of ordinary use.⁴⁶⁻⁴⁸ The size of the test area does not seem to affect the final results, although the response may be delayed if a small area is used.⁴⁹ Regarding evaluation, the scoring of ROAT reactions should be reported.⁵⁰ The evaluation of the severity of reactions can be positive, negative, or questionable. It is practically done by visual examination alone, although some bioengineering equipment, including laser Doppler velocimetry, can be used, as can the measurement of transepidermal water loss.^{51,52} In positive tests, erythematous papules, follicular papules, and vesicular lesions may occur.

As with patch testing to nonstandardized substances, testing in nonsensitized control subjects rules out irritant reactions. Testing control subjects can be considered in suspected cases of irritant reactions from a ROAT when reactions are seen after the first few applications. Several studies with various allergens have shown correlation between the elicitation threshold—the concentration giving a visible skin reaction by patch testing—and ROATs.^{47,52-56} Some studies do not show correlations between the patch test and a ROAT. The patients who had positive patch test results to lower concentrations did not necessarily have positive ROAT results.^{47,48,57-59} Individual factors, such as patch test sensitivity, regional skin reactivity, exposure dose, time of exposure, and percutaneous penetration may play significant roles on results and degree of reactivity.⁶⁰ In addition, negative results of a ROAT on normal skin may become positive on diseased skin.

Lymphocyte transformation tests

Patch testing is considered inconvenient by some patients because it requires bathing restrictions and 3

visits to a dermatologist. Patients with generalized dermatitis may not have enough unaffected skin for patch testing. The LTT is an in vitro test in which peripheral blood lymphocytes are incubated in the presence of various antigens and thymidine for 7 days. The hapten-specific T cells in sensitized individuals proliferate, indicating sensitization.⁶¹ The LTT may represent a helpful tool to detect the cause of allergic contact sensitization. LTTs have some advantages of an in vitro test and none of the risks of patch testing. LTTs have been performed to assess sensitizations to drugs, nickel, and other metals.⁶²⁻⁶⁸

Hagemann et al⁶⁹ reported a LTT in a patient with minoxidil allergy, which was helpful because minoxidil may cause irritant reactions. LTTs may be considered in the diagnosis of ACD in some situations; for example, p-phenylenediamine (PPD) and its derivatives are strong allergens, and iatrogenic sensitizations and severe patch test reactions to PPD may occur. In addition, a LTT may be used to test some contact allergens with unknown potential toxicity.⁷⁰

Attempts to use peripheral blood for in vitro testing have had limited success. The nonspecific proliferation of lymphocytes in the presence of nickel can occur, and we cannot conclude that a LTT is a standard test for clinically relevant sensitization to metals.⁷¹ Factors including timing of the LTT in relation to epicutaneous testing or accidental exposure need to be considered. The limitations of a LTT include its sensitivity, limited availability, and the limited number of allergens that are tested. A combination of LTT and the measurement of various cytokines released by lymphocytes has been used to better help assess ACD.⁷²⁻⁷⁴

The diagnosis and management of metal hypersensitivity reactions to implanted devices remains challenging and controversial. Patch testing is considered the criterion standard for diagnosing ACD on the skin, and a LTT is a way to evaluate the reactions of circulating lymphocytes (ie, it is not specifically targeted to the skin) with some concerns regarding its reproducibility and relevance. A positive patch test to a metal component of the implant is 1 of 4 major criteria, and a positive in vitro test to metals (ie, LTT) is 1 of 5 minor criteria for metal hypersensitivity reactions to metallic implants published previously.⁷⁵ These criteria may be useful for guiding decision-making. Ultimately, the decision regarding further intervention and the use of an alternate material in a subsequent device replacement depends on the patient and the surgeon. LTT may be considered in doubtful/questionable cases; however, its clinical significance in implant intolerance remains to be established and validated.⁷⁶

The subject of metal hypersensitivity to implanted devices continues to be studied and debated.

Atopy patch tests. It has been previously reported that patients with AD do not have a predisposition to develop ACD. However, more recent studies have shown at least similar prevalence or higher prevalence of contact sensitization in AD compared with non-AD (depending on allergens).⁷⁷⁻⁷⁹ The prevalence of contact sensitization to certain chemicals used in topical products (ie, fragrances, ethylenediamine, and neomycin) was higher in individuals with AD and filaggrin mutation when compared with filaggrin nonmutation carriers without AD. The same study from Denmark also found that contact sensitization to ≥ 1 allergen, but not nickel and thimerosal, was significantly associated with AD (odds ratio, 2.53). Thimerosal and nickel sensitization were excluded because these contact allergies are typically caused by vaccination and ear piercing, both of which bypass the epidermis. Nickel and thimerosal sensitization was similar in individuals with and without filaggrin mutations.⁸⁰

Sensitization to certain antigens may be even more common in patients with AD. In vitro predictive tests of T cell-mediated immunity usually fail to recognize antigens that may use antigen-specific immunoglobulin E (IgE) in the presentation process, such as proteins and propylene glycol. Atopy patch tests (APTs) are performed by applying protein allergens—usually used to elicit standard IgE-dependent reactions tested by the skin prick test, such as foods and aeroallergens—in an occlusive chamber for 48 hours.⁸¹ Although all aspects of AD are not the result of allergy, the diagnostic criteria for AD were modified by Hanifin and Rajka⁸² in 1980 to include positive skin prick test results for food and/or airborne allergens as minor criteria. APT results are evaluated at 48 to 72 hours after application. The sensitivity and specificity varies widely depending on the allergen(s).⁸³ The mechanism of an APT is not exactly the same as skin prick tests or conventional patch tests because it is thought to be IgE-dependent but cell-mediated.⁸⁴ When allergen is captured by IgE, it binds to the IgE receptor on antigen-presenting cells. Antigen presentation results in a T cell-mediated allergen specific immune response, which is responsible for the eczematous reaction.⁸⁵ Positive APTs in patients with AD indicate hypersensitivity to food and inhalant allergens as a possible trigger of skin lesions.⁸⁶⁻⁹⁰

The relationship between AD and food allergy is evidenced by the provocation of AD flares by foods in some children with AD.^{86,88} Because of barrier dysfunction and drooling, atopic infants often have perioral irritant dermatitis. This may exemplify

cutaneous sensitization via inflamed perioral skin leading to food allergy. Ingestion of the food can cause exacerbation of AD. In this sense, food allergy in patients with AD can be considered a type of SCD. Double-blind, placebo-controlled food challenges (DBPCFCs) remain the criterion standard for diagnosing food allergy. However, the patient must remain in a controlled environment for at least 48 hours to assess for flares of dermatitis. This makes DBPCFCs for delayed-type hypersensitivity both time- and cost-prohibitive.

Skin prick tests seem to reflect IgE-mediated or early reactions to food challenges, whereas the APT may have a diagnostic efficacy for late phase reactions.⁹¹ Previous studies have confirmed the usefulness of APTs for diagnosing cow's milk, hen's egg, wheat, and soy allergies.^{91,92} However, some studies found its role controversial because APTs conducted with food are not standardized.⁹³⁻⁹⁵ Patients with atopic dermatitis may have a lowered irritant threshold, contributing to false-positive patch tests. Microbial proliferation in patch tests may also trigger AD.

Children with atopic dermatitis develop flexural contact dermatitis around the time they begin to play outdoors. Some of them have exacerbation of skin lesions after contact with or inhalation of aeroallergens (ie, house dust mites, pollen, or animal dander) and improve after avoidance.^{90,96} Positive APT results to aeroallergens are found more frequently in patients with eczematous lesions in an air-exposed pattern.⁹⁶⁻⁹⁹ Previous studies revealed low sensitivity of APTs for aeroallergens (18-66%) and higher specificity (64-91%) compared to skin prick tests (50-85%) and serum IgE (52-85%).^{89,97} Although positive APT results to house dust are also encountered in individuals without AD, their frequency and intensity are lower compared to patients with AD, and may be irritant responses caused by protease content.^{100,101}

APTs require standardization but may provide more diagnostic information than the detection of purely IgE-mediated sensitization. Patients with AD who do not respond to treatment should be evaluated for precipitating factors, such as food and aeroallergen hypersensitivity, in addition to evaluation for conventional contact dermatitis and infections. Allergen avoidance may subsequently lead to a decrease in the exacerbation of AD and help prevent unnecessary diet restriction based solely on skin prick tests.

NEW/EMERGING ALLERGENS

Advances in technology and the continually evolving nature of industry results in the introduction

of many new chemicals into the environment and personal care products. This results in new consumer exposure and potential new allergens. The number of new products developed annually is substantial; the number of new allergens is sizeable. Clinicians must be aware that new, yet to be described allergens may be responsible for a patient's ACD. Only with investigative work by the patient, physician, and in certain cases, the patient's employer can one determine the new allergen. With the continuous development of new chemicals, dermatologists play a critical role in discovering and reporting novel allergens. Most of the new allergens discovered are reported in case reports or series.

Dimethyl fumarate is the perfect example of a new allergen that led to widespread consumer exposure. It was not until dermatologists identified the problem and then isolated the responsible chemical that the outbreak was solved.¹⁰² In 2007, several cases of ACD were discovered in Finland that were caused by fabric from a chair and couch that were manufactured in China. Over the next year, cases were reported in other countries. Expert dermatologists in the field of ACD eventually discovered the cause to be dimethyl fumarate. This chemical, contained in small sachets placed in the furniture, was being used as an antifungal agent. The investigative work of dermatologists means that dimethyl fumarate is unlikely to be a major cause of ACD in the future. The evidence was so strong and overwhelming that use of this allergen by manufacturers has essentially stopped. In addition, the European Union banned the import of any products with dimethyl fumarate, and as a result this allergen is no longer a problem.¹⁰²

Sorbitans, which are emulsifiers, have been around for many years, and their ability to cause ACD has been well documented. Sorbitan as a cause of ACD has been an emerging problem because they are widely used in topical corticosteroid preparations.¹⁰³

In addition to new allergens, common allergens evolve over time. ACD to fragrances is well documented. Because of the plethora of fragrance chemicals found in consumer products, it is not feasible to patch test an individual to each and every fragrance available. Mixtures of fragrances have been developed as screening tools to detect an underlying fragrance allergy. The first fragrance mixture (fragrance mix I) was developed in the late 1970s and has been shown to be a good screening agent for underlying fragrance allergy. Approximately 75% of individuals with a fragrance allergy will react to fragrance mix I.¹⁰⁴ *Myroxylon pereirae* has been around longer and is also used as a screening agent for fragrance products. Approximately 50% of

individuals with a fragrance allergy will react to this chemical. In an attempt to stay abreast of the new fragrance chemicals introduced into consumer products and increase the ability to detect fragrance allergies with screening allergens, fragrance mix II was developed. When compared with fragrance mix I, the new mix was able to detect a higher percentage of individuals than fragrance mix I alone.¹⁰⁴ Studies have estimated that fragrance mix II increases the ability to detect fragrance allergy by 10% to 28%.^{104,105} As more fragrances are brought to market, clinicians will need to continually monitor and adjust testing mixtures to achieve the best overall yield from patch testing.^{104,105}

Recent attention has been given to a resurgence of methylisothiazolinone (MI) as a contact allergen. This preservative has been known to be a cause of ACD for decades. Typically methylchloroisothiazolinone (MCI) and MI have been patch tested together in a mixture of MCI/MI. More recently, MI has been used on its own, resulting in cases of ACD.¹⁰⁶ Because MI is now being used as a stand-alone preservative in various cosmetic and personal care products, it is recommended to patch test to the combination of MCI/MI and MI alone. Some cases of MI allergy will not be detected with the mix in part because when used alone, MI is used at a higher concentration than when used with MCI; when tested alone, it is tested at a higher concentration than when tested with MCI.^{106,107}

Old allergens sometimes become allergens with more current relevance. Nickel exposure through cell phones, an increasing number of body piercings, and the metal allergy in stenting procedures has brought to light a renewed interest in nickel allergy.¹⁰⁸ Regulation of nickel in other countries has led to decreases in nickel sensitivity. To date, this has not occurred in the United States.¹⁰⁸ PPD, commonly known as a hair dye allergen, also had renewed interest when this chemical was found in temporary henna tattoos. The adulteration of henna tattoos with PPD to prolong duration and enhance the color led to several reports of ACD in vacationers.¹⁰⁹ These 2 "older" allergens took on new relevance in these current settings.

Table IV is an abbreviated list of some new or emerging allergens that have been reported in the last several years.

The field of ACD is continually evolving as new allergens are introduced into the marketplace and therefore into our patients' environments. Clinicians must remain ever vigilant to the possibility of ACD and patch test when appropriate so as to best manage and treat patients with suspected contact dermatitis. This simple in-office procedure can be

Table IV. Newly reported or emerging allergens in the last 10 years¹¹⁰⁻¹²³

2-hydroxyethyl salicylate
Aliphatic polyisocyanates
Bisabolol
Butylhydroxytoluene
Carmine
Cetyl alcohol
Decyl glucosides
Dimethyl fumarate
Majantol
Methyl aminolevulinate
Methylene bis-benzotriazolyl tetramethylbutylphenol
Octyldodecyl xyloside
Peppermint
Sorbitans
Uranyl acetate
Sodium dehydroacetate

extremely valuable in the resolution of chronic dermatoses.

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Allergic contact dermatitis



Patient management and education

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Learning objectives

After completing this learning activity, participants should be able to counsel and educate patients with allergic contact dermatitis by utilizing tools available to dermatologists and identify emergent allergens not available on standard testing series.

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Allergic contact dermatitis is a common diagnosis resulting from exposure to a chemical or chemicals in a patient's personal care products, home, or work environment. Once patch testing has been performed, the education and management process begins. After the causative allergens have been identified, patient education is critical to the proper treatment and management of the patient. This must occur if the dermatitis is to resolve. Detailed education is imperative, and several resources are highlighted. Photoallergic contact dermatitis and occupational contact dermatitis are other considerations a clinician must keep in mind. (J Am Acad Dermatol 2016;74:1043-54.)

Key words: allergen; allergic contact dermatitis; eczema; occupational contact dermatitis; patch testing; photoallergic contact dermatitis; systemic contact dermatitis.

The identification of allergens in a patient diagnosed with allergic contact dermatitis (ACD) is the first step in patient management. Patient education follows, and is vital to the successful treatment and management of the patient. Part II of this continuing medical education article reviews education of the patient, including important resources, the management of complications, a discussion of photoallergic contact dermatitis (PACD), and an introduction to the complex and

Abbreviations used:

ACD:	allergic contact dermatitis
ACDS:	American Contact Dermatitis Society
BRM:	black rubber mix
NACDG:	North American Contact Dermatitis Group
OCD:	occupational contact dermatitis
PACD:	photoallergic contact dermatitis
PCP:	personal care product
PPD:	para-phenylenediamine
SCD:	systemic contact dermatitis
ROAT:	repeat open application test

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challenging subject of occupational contact dermatitis (OCD).

PATIENT EDUCATION

With regard to successful patient management, patient education regarding the allergens identified through patch testing is as important as identifying the allergens themselves. It is imperative that patients be educated about all allergens identified during the patch test procedure. This information should be both oral and written and include instruction on label reading, written materials discussing where the allergens can be found, relevant synonyms that might be used, and how to avoid the allergens. Simply supplying a patient with the names of any identified allergens is not adequate. Time must be taken for detailed patient education or it is unlikely that the patient's dermatitis will improve even after discovering the causative allergens. Educating patients about the allergens identified and their potential current, past, and future relevance is important for patients to clear current dermatitis and avoid future problems with the allergens.

Written materials sent before patch testing can be helpful in preparing the patient for the patch testing procedure. Information describing the procedure, including patch testing basics, can lay the foundation for the education process even before patch testing begins. Many patients are misinformed and believe that patch testing and skin scratch/intradermal testing are identical. Patients need to be educated that patch testing is a delayed-type hypersensitivity reaction that differs from skin prick testing, which tests for an immediate hypersensitivity reaction.¹⁻³ The former typically leads to skin rashes; the latter leads to rhinorrhea, eye tearing, and shortness of breath.⁴

Patch testing identifies allergens that come into direct contact with the skin (ie, those found in personal care products [PCPs], such as fragrances, preservatives in soaps, lotions, and shampoos) and items worn on the skin (ie, metals [jewelry, belt buckles, zippers, snaps, and cell phones], rubber additives [gloves, shoes, and elastic in clothing], or textiles [dyes/formaldehyde resins]). In addition, topical drugs—both over the counter and prescription varieties—can contain allergens in the inactive or active ingredients of the products.

Grouping allergens can make it easier for patients to understand what they are and where they are found (Table I). Carba, thiuram, and black rubber mixes (BRMs) are rubber allergens. Disperse blue 106 and melamine formaldehyde are clothing allergens. Tixocortal pivalate and budesonide are cortisone allergens. Quaternium-15, fragrance, and

Table I. American Contact Dermatitis Society core allergens grouped into main categories*

Allergen	Allergen type
Core allergen panel I	
Nickel sulfate	M, S
<i>Myroxylon pereirae</i>	f, P, S
Fragrance mix I	f, P, S
Quaternium 15	P
Neomycin	m
Budesonide	m, c
Formaldehyde	P, S, T
Cobalt chloride	M, S
p-tert-Butylphenol formaldehyde resin	A
p-Phenylenediamine	P
Core allergen panel II	
Potassium dichromate	M, P, S
Carba mix	R, T
Thiuram mix	R, T
Diazolidinyl urea	P
Paraben mix	P, S
Black rubber mix	R, T
Imidazolidinyl urea	P
Mercapto mix	R, T
Methylchloroisothiazolinone/ methylisothiazolinone	P, R
Tixocortal-21-pivalate	m, c
Core allergen panel III	
Mercaptobenzothiazole	R, T
Colophony	A, P
Epoxy resin	A
Ethylenediamine	R, S, T
Wool alcohol	P
Benzocaine	m
Bacitracin	m
Mixed dialkyl thioureas	A, R, T
Fragrance mix II	f, P, S
Benzophenone-3	P, Su
Core allergen panel IV	
Disperse blue 106	T
Disperse blue 124	T
Gold sodium thiosulfate	M
Ethyl acrylate	A, P
Compositae mix	P, pl, S
Sesquiterpene lactone mix	P, pl, S
DMMD hydantoin	P
Tosylamide formaldehyde resin	P
Methyl methacrylate	A, P
Cinnamic aldehyde	f, P, S
Core allergen panel V	
Propylene glycol	P, S
Cetyl steryl alcohol	P
2-Bromo-2-nitropropane-1,3-diol	P
Sorbitan sesquioleate	P, S
Cocamidopropylbetaine	P
Glyceryl thioglycolate	P
Ethyleneurea melamine-formaldehyde	T
Iodopropynyl butylcarbamate	P

Continued

Table I. Cont'd

Allergen	Allergen type
Chloroxylenol (PCMX)	P
Glutaraldehyde	d, P
Core allergen panel VI	
Ethyl cyanoacrylate	A, P
Benzyl alcohol	f, P, S
Benzalkonium chloride	d, P
Methyldibromoglutaronitrile	P
Propolis	P
n,n-Diphenylguanidine	R, T
Lanolin alcohol (Amerchol 101)	P
Triethanolamine	P
Amidoamine	P
Desoximethasone	m, c
Core allergen panel VII	
Triamcinolone	m, c
Clobetasol-17-propionate	m, c
Hydrocortisone-17-butyrate	m, c
4-Chloro-3-cresol (PCMC)	P
Benzophenone-4	P, su
Chlorhexidine digluconate	d, P
Ylang ylang	f, P
Phenoxyethanol	P
Sorbic acid	P, S
2, 6-Ditert-butyl-4-cresol (BHT)	P, S
Core allergen panel VIII	
Disperse orange 3	T
3-(Dimethylamino)propylamine (DMAPA)	P
Oleamidopropyl dimethylamine	P
Dl alfa tocopherol	P, S
Cocamide DEA	P
Lidocaine	m
Dibucaine	m
Jasmine absolute	f, P
Tea tree oil	f, P
Triclosan	P

A, Adhesive; c, corticosteroid; d, disinfectant; f, fragrance; m, medication; M, metal; P, personal care product; pl, plant; R, rubber; S, systemic (ingested) allergen; su, sunscreen; T, textile.

*This table is not meant to be an exhaustive grouping of allergens into various categories, but rather to give examples of some ways to consider allergen function for patient education.

methylisothiazolinone (MI) are all PCP allergens. The PCP allergens can be further divided into categories, such as preservatives (eg, methyldibromoglutaronitrile, MI, iodopropynyl butylcarbamate, and paraben mix), fragrance screening chemicals (eg, fragrance mixes I and II and *Myroxylon pereirae*), surfactants (eg, cocamidopropyl betaine), and emulsifiers (eg, sorbitan sesquioleate).

Many allergens have >1 function. For example, ethylenediamine is a stabilizer used in cosmetics but also in latex emulsion.⁵ Colophony, a pine tree derivative, is used in adhesives, cooling fluids, hair removal wax, and can be a screening chemical for

fragrance allergy.⁵ Formaldehyde can be used as a preservative, in synthetic rubber production, textiles, leather tanning, and dental plastics.^{5,6} Patients who are allergic to formaldehyde also need to be educated about formaldehyde-releasing preservatives (FRPs) found in shampoos, body washes, lotions, and some corticosteroids, such as Quaternium-15, 2-bromo-2-nitropropane-1,3-diol (bronopol), imidazolidinyl urea (imid urea), diazolidinyl urea, and 1,3-bis(hydroxymethyl)-5,5-dimethylimidazolidine-2,4-dione (DMDM hydantoin).

It is important for patients to understand the functions of their allergens so they can better assess where they are found and how to comply with avoidance. To show the importance of this, one should consider the formaldehyde-sensitive patient who has a diffuse truncal rash but is not using any PCPs with FRPs. This patient should be informed that permanent press/wrinkle-resistant fabrics can release formaldehyde, and formaldehyde in clothing could therefore be contributing to the dermatitis.

Patch testing investigates allergy to many chemicals. Some chemicals can indicate allergy to other structurally related chemicals. For example, the hair dye chemical p-phenylenediamine (PPD) and BRM are often used to test for textile dye allergens because of structural similarities between these and certain disperse dyes. In 1 study, PPD and BRM detected approximately 50% of patients allergic to ≥1 ingredient of a textile dye mix.⁷ Similarly, a patient who is allergic to neomycin could also react to gentamycin and tobramycin given their structural similarities to neomycin.⁵

Chemicals that can be used to help detect fragrance allergy include cinnamic aldehyde (on the North American Contact Dermatitis Group [NACDG] standard but not on the Thin-layer Rapid Use Epicutaneous [T.R.U.E.] Test [SmartPractice, Phoenix, AZ]), fragrance mix I (a NACDG standard and T.R.U.E. Test allergen), fragrance mix II (on the NACDG standard but not on the T.R.U.E. Test), and *Myroxylon pereirae* (a NACDG standard and T.R.U.E. Test allergen). One study found that patients who were allergic to fragrance mix I had coreactions to various other fragrance chemicals not present in the mix.⁸

Allergy to fragrance mix I was detected in 8.5% of the approximately 4300 patients with dermatitis who were tested by the NACDG.⁹ Allergy to *Myroxylon pereirae* was detected in 7%, and allergy to fragrance mix II in 5% of the NACDG patients with dermatitis.⁹ This indicates that fragrance allergy represents a significant allergen. Patients are frequently reacting to fragrances within PCPs.¹⁰ Unfortunately for consumers, even items labeled as "fragrance-free," "sensitive skin," "dermatologist-tested," and "for

“baby” are often not truly fragrance-free.¹¹ It is essential to have patients bring in all of their PCPs to help them with the label-reading process. Patients need to be educated that even products labeled “fragrance-free” can contain fragrance chemicals, such as farnesol, benzyl alcohol, benzaldehyde (the latter 2 are components of *M pereirae*), and various essential oils of flowers.¹² Maltol, an ingredient in some soaps, occurs in pine needles and the bark of larch trees and is a fragrance/flavoring.¹³ If ingredients are not used “solely to impart an odor to a product” but are instead used as emollients or have other functions, it is legal for a “fragrance-free” product to contain fragrance.¹¹ There are 2 helpful databases that simplify this process as cross-reactors are removed from the list of safe products, making avoidance easier for patients: the Contact Allergen Management Program (CAMP) and the Contact Allergen Replacement Database (CARD).

In the United States, fragrances are listed generically on product labels as “fragrance,” making avoidance difficult. As a result of this labeling process, if patients test positive to fragrances they must, at least initially, avoid all fragrances until clearing of the dermatitis occurs and then add 1 product back every 1 to 2 weeks, if so desired. The European Union has identified 26 fragrance chemicals that, since 2005, must be labeled on cosmetic products.¹⁴ Studies have shown that testing to this list helps identify relevant fragrance allergens.^{15,16} This also assists patients in identifying products containing known allergens and may make fragrance avoidance to these 26 chemicals easier to follow. This labeling practice is not yet standard in the United States.

RESOURCES

Given the complexity of information a patch test patient may receive, it is helpful to provide them with written information for future reference. *Contact and Occupational Dermatology*⁵ contains handouts specifically created for teaching purposes, and these sheets can be distributed to patients. Some manufacturers and organizations include allergen information on their websites, such as Chemotechnique (www.chemotechnique.se), T.R.U.E. Test (www.truetest.com), Smart Practice (www.allergeaze.com), the American Contact Dermatitis Society (ACDS) (www.contactderm.org) and Preventice (www.allergyfreeskin.com).

A given patient’s educational level and literacy need to be considered.¹⁷ Patients with lower literacy levels are less likely to understand printed material and more likely to have difficulty controlling chronic illnesses.^{17,18} Tests are available to help determine a patient’s literacy level, and these can be easily

administered in the office.¹⁷ Patient information should be written at a sixth grade or lower reading level.¹⁷ In addition to providing easily understandable materials, health care providers must also provide concrete ways to put clinical recommendations into practice, otherwise known as “actionability.”^{19,20} Demonstrating label reading can be useful. Studies have shown that recall of easily understandable material is poor, even in individuals with high literacy levels and even after repetition.^{21,22}

Cognitive theory recommends minimizing extraneous information to improve memory and prevent memory overload.²³ This means that printed patch test materials should be concise, written in simple language, and use lists or pictures when possible.²³ Patients should be instructed to keep the handouts and review them periodically. Free videos describing specific allergens can be accessed at www.mypatchlink.com.

There are benefits and disadvantages to both print- and video-based health materials.²³ For procedural content (ie, the patch test procedure), a video may be the most effective tool. However, for actions that need to be practiced on a long-term basis to control a chronic disease (ie, ongoing avoidance of identified allergens), print information may be preferable for longer recall so that patients can refer to the information. If patients are not improving within 4 to 6 weeks after patch testing, it is worthwhile to review allergens and avoidance strategies to make sure they are in compliance with allergen avoidance and understand the process.

Two large databases provide lists of “safe” products that are free of allergens identified during patch testing (CAMP and CARD). These can be printed or emailed for patient use.

CAMP is a member benefit of the ACDS and contains approximately 5000 products. Most CAMP products are found in major American drug stores. CAMP product ingredients are checked by hand before being entered into the database and are updated every 1 to 1.5 years. A quality assurance committee of the ACDS reviews approximately 1% of CAMP products annually for accuracy. Products are grouped into categories, such as antiaging creams, hair dyes, moisturizers, shampoos, soaps, sunscreens, and prescription medications, to name a few. This provides patients with an easily accessible list of products that are safe to use. Reading the labels of all PCPs to confirm that a product is free of a known allergen is still encouraged, but this list makes product selection easier for the patient. Patients can also be given a unique access code that allows them to update their CAMP lists directly at www.acdscamp.org and via the ACDS CAMP app,

free of charge. An in-depth, step by step guide to using CAMP can be found on the ACDS website.

Physicians can pay for a yearly subscription to CARD, and patients can get access to their CARD listing for a monthly fee after a 6-month free trial. CARD is maintained by the for-profit group Preventice and contains approximately 5500 products.

ACD can occur 24 to 48 hours after exposure; patients are therefore often unaware that a favorite PCP is causing their rash.²⁴ Even products that have been used for years can result in dermatitis either because of a change in the product formulation or as a result of sensitization to the product over time.²⁵ An important contributing factor in the development of ACD is decreased skin barrier function.²⁶ Decreased environmental humidity, sweating, friction, heat, and exposure to skin irritants can all enhance ACD in a sensitized individual. Patients with disrupted barrier function (eg, poorly controlled patients with atopic dermatitis or patients with leg ulcers and chronic dermatitis) are at risk of sensitization to even weak allergens.²⁷⁻³⁴

The labels on all of a given patient's PCPs should be read to determine if an identified allergen is present. In addition, it is important for patients to bring in their PCPs for testing. Failure to test with a patient's PCP can miss a causative allergen. A repeat open application test (ROAT) or use test can be performed with leave-on products to verify that a product is safe to use. A ROAT involves twice daily application of a leave-on product to see if a rash develops.^{35,36} If no dermatitis occurs, one can assume that the product is safe to use. However, there can be false-negative results with a ROAT, especially if the product in question has been applied to nondiseased skin.³⁵ For topical corticosteroids, a ROAT may need to be performed for ≤ 2 weeks because the corticosteroid can suppress reactions to itself. Wash-off products cannot be tested "as is" because they are not meant to be left on the skin. These products need to be diluted, and there are excellent resources for diluting them.³⁷ Provocative use testing is another way to determine relevance: this involves applying a small amount of the product in question to the area of typical use and observing for a reaction.

The relevance of any reaction needs to be determined and discussed with the patient. There are times that clinical relevance can only be ascertained weeks after testing.³⁸ For example, a patient with hand dermatitis who is found to be allergic to carba mix and who has a history of wearing rubber gloves to wash dishes needs to know that carba mix can be present in natural and synthetic rubbers, such as the gloves being worn to wash dishes. If the

patient's hand dermatitis resolves with avoidance of these rubber gloves, it provides empiric evidence of clinical relevance of the positive patch test reaction. However, positive reactions may simply represent past sensitization and may not be clinically relevant. For example, a patient with scalp dermatitis and a positive reaction to gold on patch testing but no history of gold exposure does not have clinical relevance of the gold patch test reaction to the scalp dermatitis. Gold and thimerosal are frequently positive, but not always relevant, and as a result, the NACDG no longer includes either of these T.R.U.E. Test allergens in their standard series, citing infrequent relevance with the exception of eyelid dermatitis and gold allergy.^{9,39,40} Some allergens, such as parabens and lanolin, are paradoxical—they may be allergenic on dermatitic skin but tolerated on intact skin.⁴⁰⁻⁴² Gold, a common allergen in patients with eyelid dermatitis, is often tolerated under jewelry, but can cause eyelid dermatitis when transferred from the fingers to the eyelids.^{43,44}

SYSTEMIC CONTACT DERMATITIS

A patient sensitized to a "topical" allergen can develop systemic contact dermatitis (SCD) if exposed to that allergen via a non-skin surface route (ie, ingestion, parenteral, suppository, implanted, and inhaled).⁴⁵ Dermatitis can manifest as oral, anogenital, flexural, fixed, reactivation of a previous positive patch test site or flare of previous dermatitis, vasculitic lesions, vesicular hand dermatitis, or a widespread dermatitis.⁴⁵⁻⁵⁶ Patients with proven contact allergens who are exposed to their allergen systemically can develop noncutaneous symptoms, such as fever and sepsis-like manifestations, chest pain, or urticaria.⁵⁷⁻⁵⁹

Medications, including antibiotics, corticosteroids, antifungals, and antiepileptics, can cause SCD, as can implants and metals (eg, mercury, gold, nickel, chrome, cobalt, and titanium), plants (eg, chamomile, chrysanthemum, and other members of the Compositae family), mango, garlic, and shiitake mushrooms.⁴⁵ Additional allergens that have both topical and potential ingested exposure sources include propylene glycol, parabens, butylated hydroxyanisole and cross-reacting butylated hydroxytoluene, sorbic acid, benzoic acid, sodium benzoate, formaldehyde, sorbitan sesquioleate (sorbitol), gallates, and fragrance/flavoring.⁴⁵ The interested reader is referred to an excellent review article by Veien⁴⁵ for more in-depth reading on this subject.

In patients who are not improving with the cutaneous avoidance of allergens, dietary avoidance may help.^{60,61} Approximately 50% of fragrance-allergic patients, in 1 study, improved while adhering

Table II. Potential side effects of patch testing

Occurrence	Side effect
Common	Itching at site of patch testing
	Pruritus
Rare	Tape irritation
	Anaphylaxis
	Angry back syndrome
	Infection
	Koebnerization
	Persistent patch test reaction
	Scarring
	Sensitization

to a diet that was low in balsam.⁶² Nickel, chromium, and cobalt are present in many foods.⁶³⁻⁶⁶ Reviewing various oral challenge studies, Jensen et al⁶⁶ found that patients with SCD to nickel can react to ingested nickel in a dose-dependent fashion. The most sensitive of nickel-allergic patients can react to normal amounts of nickel in water and diet (0.22-0.35 mg).⁶⁶ A point-based system of foods that may be eaten in the setting of SCD to metals has been suggested for nickel-, cobalt-, and chromium-allergic patients.^{67,68} Sharma⁶⁹ delineates food avoidance strategies for chromium-allergic patients.

PATCH TEST SIDE EFFECTS

Serious side effects from patch testing are infrequent. Side effects fall into 2 major groups. The first type of side effect is common and expected, such as pruritus at the site of a positive reaction. The second type of side effect is rare but serious, including sensitization to the patch test allergen, infection, and anaphylaxis (Table II). Extensive research has been conducted to determine that the correct concentrations of allergens are applied. Most side effects from patch testing are anecdotal.

In rare cases, a patient may develop widespread, multiple, positive patch test reactions. This phenomenon has been termed angry back syndrome (ABS)⁷⁰ and is also known as excited skin syndrome. Excited skin syndrome may be the preferred term because the entire skin is hyperexcitable.^{71,72} This reaction must be distinguished from individuals that have multiple positive patch tests (ie, multiple reactors). Multiple reactor patients have allergen reactions that appear to be clinically relevant and related; most reactions in patients with ABS are eventually deemed clinically irrelevant.

Angry back syndrome

ABS is uncommon, poorly understood, and poorly studied. It appears that the reactions are not reproducible within any given patient.⁷³ This

hyperirritability may more likely be caused by allergens that act as both irritants and allergens, and in a small subset of patients ABS occurs.⁷⁴ Perhaps irritants can cause secondary weak to moderate positive patch test reactions in the correct individual and under the correct physiological conditions.⁷⁴

A combination of a fluctuation in cellular and humoral immunity, irritancy, nonimmunologic factors, and other unknown factors play a role in its development.⁷³ Some authors indicate that ABS is caused by a severe allergic relevant reaction at 1 site with spreading (spillover) to other patch test sites. The typical presentation is seen after the patch tests are removed for the first reading. Widespread positive reactions will be seen. There is often 1 severe patch test reaction and multiple positive reactions in close proximity to the most severe reaction. Characteristically, the reactions are across many classifications of allergens; multiple reactors are more likely to have multiple reactions within a class of allergens (eg, the formaldehyde class).

In 1 study of 5 patients, ABS was not reproducible.⁷³ Clinicians need to be aware of this potential reaction and differentiate it from the patient with multiple relevant reactions. In patients with ABS, patch testing again in 2 to 3 months seems a reasonable approach if clinically warranted.⁷⁵ In exceedingly rare situations, patients will have near universal positivity to all patch test sites. In these cases, one must consider an allergy to the vehicle or the Finn chamber, which is composed of aluminum.⁷⁶

Persistent patch test reactions

Another rare potential side effect of patch testing is the persistent patch test reaction. These reactions typically occur during the first week of application and can persist for ≥ 30 days. These reactions are most likely underreported by patients, and the true incidence is unknown. The mechanism of how these persistent reactions occur is unknown. An interaction with antigen-presenting skin cells is likely to play a role. One theory is that the antigen-presenting cells may act by sequestering the antigen within the skin, allowing a persistent reaction to occur.⁷⁷

One of the most commonly reported allergens to cause persistent patch test reactions is gold, in the form of gold chloride or sodium gold thiosulfate.⁷⁷⁻⁷⁹ Other reported causes of persistent patch tests include phenylephrine, methyl methacrylate, and textile dyes. Other than with gold salts, this is an exceedingly uncommon event.⁸⁰⁻⁸²

Sensitization

Active sensitization of a patient directly caused by the application of allergens during patch testing is,

for the most part, an exceptionally uncommon reaction, and almost never occurs at the standardized patch test concentrations that have been established over many decades. There are many sources to obtain standardized patch test concentrations to minimize and remove this potential side effect.^{5,83,84} The exact rate of active sensitization induced by patch testing is unknown, but it is felt to be rare and estimated to occur in 0.1% of patients tested.^{85,86} It may be underreported because patients may not be aware of a late reaction, or they may attribute it erroneously to a known reaction that occurred during their patch test readings. Although rare, this is one of the most concerning of the potential side effects of patch testing, because clinicians are trying to help their patients avoid allergens. Active sensitization results in another allergen that must be avoided.^{86,87}

Clinicians should consider the induction of sensitization when a patient calls 10 to 21 days after patch test application and states that they have a new reaction at a patch test site. One exception is with gold salts; these late reactions are nearly always felt to be persistent patch test reactions and not active sensitization. These late reactions can be caused by individuals that have delayed reactions (ie, slow responders and late reactors) to the allergen, or because of active sensitization, and the differentiation of these 2 possibilities is difficult.^{88,89} If the allergen that has caused this late reaction is identified, one can test for sensitization by using a $\times 10$ to $\times 100$ dilution of the allergen. This diluted allergen can then be re-patch tested, and if a positive reaction occurs within 6 days, active sensitization has most likely occurred.⁹⁰ In 1 study, PPD was felt to cause sensitization in 1.5% of those tested and epoxy resin caused sensitization in 0.3% of those individuals tested, with a 1% concentration in petrolatum for each.⁹¹ In this same study, no sensitization was found with the use of nickel sulfate. The authors of this study recommended decreasing the test concentration or time of patch test application of PPD so as to avoid sensitization. When the time of patch test application of PPD was decreased from 48 to 24 hours, the sensitization rate decreased from 1.5% to 0.3%.⁹¹ When decreasing the patch test concentration to 0.35%, a decrease in the sensitization rate of PPD was also seen.⁹²

PPD has been the most reported allergen to cause sensitization. Other allergens have also been reported, including epoxy resins, isothiazolinones, primula, acrylates, balsam of Peru, fragrance mix I, para-tertiary-butylcatechol, and Compositae mix.^{86,93-97}

Other complications and side effects

Other complications and side effects⁹⁸ of patch testing are listed below.

Pruritus. Pruritus is the most common effect of a positive patch test, and its presence is a normal reaction to a positive test reaction. It technically should not be considered a side effect, but patients should be informed of this common reaction. Pruritus is self-limited and is often easily treated with a topical corticosteroid for a few days.

Postinflammatory hyper- or hypopigmentation. As with any eczematous reaction, post-inflammatory hyper- or hypopigmentation may occur, typically in patients with darker skin. These reactions are typically mild and self-resolve.

Infections. Infections, particularly a mild impetiginization with *Staphylococcus aureus* or another bacterial agent, may cause a superinfection of the patch test site. Viral reaction of herpes simplex virus within the patch testing sites is possible but unlikely. A single case report of a deep fungal infection occurring after patch testing part of a plant has been reported.^{99,100}

Scarring. Any disruption of the dermoepidermal junction may lead to scarring. This is a highly unlikely side effect to patch testing, and is most often seen in patients with severe bullous reactions. Keloids and hypertrophic scarring have both been reported to occur, typically in individuals with an underlying predisposition or a history of previous abnormal scarring.^{99,100} Bullous patch test reactions have led to the development of milia.

Anaphylaxis. Another exceedingly rare potential side effect of patch testing is an immediate reaction leading to anaphylaxis. These reactions, if they occur, typically do so within 30 minutes of application of the patch test agents. The hair bleach ammonium persulfate is the most often reported agent; however, latex, formaldehyde, penicillin, and others have been reported.¹⁰¹⁻¹⁰⁷

Irritant tape reaction. The most common adverse effect of patch testing is irritation from the tape used to occlude the patches to the skin. This reaction is nearly always self-limited and resolves spontaneously. It may cause itching and slight discomfort. On occasion, the reaction may continue to worsen in a crescendo pattern after the adhesive tape has been removed. In these cases, clinicians should be suspicious of an allergy to a component of the adhesive tape product used in the patch testing process.

Koebnerization. In patients who undergo patch testing and who have underlying skin disorders, such as psoriasis, lichen planus, and Jessner lymphocytic infiltrate, koebnerization of their underlying dermatoses may be seen at the site of a positive patch test.^{108,109}

PHOTOALLERGIC CONTACT DERMATITIS

PACD is a rare dermatologic condition that can cause photosensitivity. PACD is a type IV hypersensitivity reaction requiring sensitization and elicitation, and it differs from ACD in that this reaction requires a chemical that is exposed to ultraviolet radiation.^{110,111} Upon exposure, there is a chemical reaction that forms a photoallergen. The active wavelength of light involved in PACD is primarily ultraviolet A. Photopatch testing is recommended as part of the workup for photosensitive patients; however, because of overlapping clinical patterns of other photodermatoses, PACD is found in 10% to 20% of patients who are tested.⁵

PACD was first described after factory workers used tetrachlorosalicylanilide antibacterial agent in soaps in the 1960s in England.¹¹² These products were removed from the market, and tetrachlorosalicylanilide is no longer a significant cause of PACD.

Patients suspected of having PACD and candidates for photopatch testing often present with an eczematous rash in sun-exposed areas with sparing behind the ear, under the chin, and under clothing. These rashes tend to last for weeks. Some individuals complain predominately of photosensitivity. In all cases, a thorough history and physical examination is warranted, focusing on both occupational and recreational photoallergic contact allergens.¹¹³

The incidence of PACD cannot be accurately determined; however, one can deduce that its incidence is low. There are many reasons for the inaccuracy in determining the incidence of PACD. There is a lack of standardized testing, testing is typically only done at highly specialized centers, and some allergens can cause PACD, ACD, and photoirritant contact dermatitis, which can make interpretation difficult, even for the most experienced clinicians.

There is no universally accepted standardized protocol for PACD testing. An international agreement on standardization of PACD would be helpful and allow for better data collection, which could be used to assess patient safety and quality care initiatives. The European Taskforce for Photopatch Testing has advocated for standardization and has done considerable work in this regard.¹¹⁴ Required equipment for PACD testing includes a standard broad-spectrum ultraviolet A light (320-400 nm)

Table III. Photopatch test procedure

Day	Procedure
1	MED testing 2 Sets of identical allergens applied
2	MED determined
3	Reading 1: preirradiation (48 hours postapplication) UVA treated to 1 set of allergens
5	Reading 2: Immediately postirradiation; cover all sites with opaque material Reading 3: 48 hrs after UVA irradiation, 96 hrs reading of nonirradiated side
7/9 (optional)	Reading 4: 96- to 128-hr reading for final UVA-irradiated side

MED, Minimal erythema dose; UVA, ultraviolet A light.

Table IV. Patch test interpretations

Irradiated side	Nonirradiated side	ACD	PACD
—	—	No	No
—	+	Yes	No
+	—	No	Yes
++	+	Yes	Yes*

ACD, Allergic contact dermatitis; PACD, photoallergic contact dermatitis.

*ACD and possibly PACD. This is controversial, and PACD should be interpreted with caution in this setting. Clinical correlation is necessary, and retesting may be required.

source that minimizes ultraviolet B light irradiation and a standalone ultraviolet B light source. Finn chambers and an allergen set (PACD standard tray) are the backbone of the testing. Various centers across the globe test different allergens, which leads to a nonstandard approach.

If the patient is being photopatch tested because of widespread dermatitis involving all photoexposed skin, phototesting is needed before the ultraviolet light exposure is performed as part of photopatch testing.¹¹⁵ This is to ascertain that the tests will be interpretable and not become diffusely red because of a lower than normal minimal erythema dose. However, PACD does not always involve all photoexposed skin. For example, if photoallergy to a sunscreen in a lip balm or hair product is causing the dermatitis, the rash may be limited to the lips or face and neck, respectively. The photopatch test procedure and interpretation is shown in Tables III and IV.

Multiple agents have been reported to cause PACD. The majority of agents fall into a few primary categories, including sunscreens (the most frequent cause of PACD), antimicrobials, fragrances, and other medications.¹¹⁶⁻¹²¹

One side effect unique to PACD is the potential for a ultraviolet light–induced burn at the site of exposure (ie, minimal erythema dose sites and or the test sites on the back). Other sources offer a more complete discussion of PACD and photopatch testing, which is beyond the scope of this review.^{110,111,113,117}

OCCUPATIONAL CONTACT DERMATITIS

Allergic or irritant contact dermatitis resulting from workplace exposures is another interesting and challenging facet of contact dermatitis. It is critical that the physician evaluating these work place injuries be well-versed in contact dermatitis but also workers' compensation protocols. Effects of personal protective equipment, vacation, and details of the job description and exposures are critical pieces of the history. The steps of the patient's job from start to finish—including all allergen exposures as part of the job function or job site—is essential information that must be obtained and sometimes requires a site visit. Material safety data sheets can be helpful in identifying the ingredients of workplace chemicals and also provide the phone number for companies when additional information is needed. The ingredient listing often omits chemicals that are present in small percentages, such as preservatives that are felt to not be toxic. Contacting the company can help identify full ingredient listings but can also be difficult to obtain because it can be considered proprietary information.

OCD is a significant cause of occupationally related disease second only to musculoskeletal work-related injury.¹²² As in non-OCD, in the occupational setting, irritant contact dermatitis is more common than ACD. Significant cost and lost work days occur because of skin disease in the workplace.¹²² However, many cases are not reported because of a lack of identification of the workplace as the problem, the lack of established reporting, and the fact that many physicians diagnose and treat these patients. OCD costs are estimated to be up to \$1 billion annually in lost wages, lost productivity, medicolegal costs, and disability payments, etc. A significant burden of disease occurs in patients suffering from OCD because of job interruption, job transfers, lost wages, economic disadvantage, and decreased quality of life.¹²²

Some of the more common occupations that have high rates of OCD include hairdressing, health care workers, construction workers, agriculture workers, and the food industry. The most common site for OCD is the hands.¹²²⁻¹²⁴

Patch testing to appropriate allergen series specific to the patient's employment can often identify the

causative allergen. With education of the patient and employer and avoidance of any identified allergens, clearance can occur. However, even with appropriate identification of allergens, many patients with OCD will not clear completely.¹¹³ In addition to understanding the specific allergens associated with particular occupations, the patch test clinician must be well-versed in issues of worker's compensation and disability. Identifying the causative allergen is the first part in the process; helping establish a workplace environment free of identified allergens and successfully processing these claims through the system can be challenging. A thorough and complete discussion of all components of OCD is important and is beyond the scope of this article. The reader is referred to other sources^{5,83,84,122-124} for a more detailed discussion of this important and broad subject.

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Emerging infectious diseases with cutaneous manifestations



Viral and bacterial infections

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Learning objectives

After completing this learning activity, the participant should be able to describe the cutaneous manifestations of emerging viral and bacterial infections and identify appropriate therapy for case studies of emerging viral and bacterial infections with cutaneous manifestations.

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Given increased international travel, immigration, and climate change, bacterial and viral infections that were once unrecognized or uncommon are being seen more frequently in the Western Hemisphere. A delay in diagnosis and treatment of these diseases can lead to significant patient morbidity and mortality. However, the diagnosis and management of these infections is fraught with a lack of consistency because there is a dearth of dermatology literature on the cutaneous manifestations of these infections. We review the epidemiology, cutaneous manifestations, diagnosis, and management of these emerging bacterial and viral diseases. (J Am Acad Dermatol 2016;75:1-16.)

Key words: *Acinetobacter baumannii*; Chikungunya; dengue; Ebola; emerging infections; HFMD; Lyme; measles; melioidosis; rickettsia; trichodysplasia spinulosa; Zika.

EMERGING VIRAL DISEASES

The endemic areas of viral diseases, their clinical manifestations, and their diagnosis and treatment are summarized in Table I.

Ebola

Key points

- **Ebola is highly virulent and contagious, and the 2014 epidemic was declared a “public health emergency of international concern”**

- **Clinical manifestations include bleeding and nonspecific macules and papules**
- **Diagnosis is by reverse transcription polymerase chain reaction**
- **Treatment is mainly supportive**

Ebola is a hemorrhagic fever disease caused by the viruses of the *Ebolavirus* genus, a member of the Filoviridae family. Ebola was first discovered in 1976 near the Ebola River in the Democratic Republic of

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Abbreviations used:

ACA:	acrodermatitis chronica atrophicans
CDC:	Centers for Disease Control and Prevention
CVA6:	coxsackievirus A6
DHF:	dengue hemorrhagic fever
E71:	enterovirus 71
ELISA:	enzyme-linked immunosorbent assay
EM:	erythema migrans
HFMID:	hand foot and mouth disease
HGA:	human granulocytotropic anaplasmosis
HME:	human monocytotropic ehrlichiosis
MDR:	multidrug resistant
MRSA:	methicillin-resistant <i>Staphylococcus aureus</i>
PCR:	polymerase chain reaction
PRNT:	plaque reduction neutralization test
RMSF:	Rocky Mountain spotted fever
RNA:	ribonucleic acid
RT-PCR:	reverse transcriptase-polymerase chain reaction
STI:	soft tissue infections
TB:	tuberculosis
TIBOLA:	tick-borne lymphadenopathy
TSPyV:	trichodysplasia spinulosa-associated polyomavirus
WHO:	World Health Organization

Congo. Since then, outbreaks have appeared sporadically in Central Africa. The largest epidemic in history occurred in 2014, affecting multiple countries in West Africa.¹¹ Five different ebolaviruses are known, with *Zaire ebolavirus* being the most virulent and causative agent in the most recent epidemic.¹² With a fatality rate of $\leq 90\%$, the World Health Organization (WHO) declared Ebola a “public health emergency of international concern.”¹³ In January 2016, the WHO declared the end of Ebola transmission in all West African countries.¹⁰ In the US, 2 imported cases, including 1 death, and 2 locally acquired cases in health care workers were reported. Ebola can be transmitted via direct contact with body fluids. Dermatologists should be cautious of the high risk of contamination through skin biopsy specimens and dermatologic examination because of the virus’ high virulence.

Skin findings begin 4 to 5 days after fever, starting with nonspecific macules and papules.¹² Pinpoint papules are first observed around hair roots¹⁴ and are seen on the proximal extremities and can extend centrally. The rash progresses to a diffuse erythroderma. In darker skin, fine scaling has been described. Ebola causes a high rate of cell death, leading to heavy internal hemorrhage. Bleeding is frequently observed, causing petechiae, purpura, ecchymoses (Figs 1 and 2), and hematomas, particularly around needle or puncture sites.¹⁵

Infection initially presents with sudden nonspecific flu-like symptoms.¹⁵ Ebola is often deadly and

runs its course in 14 to 21 days. Acute phase detection of viral RNA by reverse transcriptase-polymerase chain reaction (RT-PCR) is the standard method of diagnosis and is vital for prognosis.¹⁶

Management is centered on supportive care with hydration, transfusion (when available), and critical care.¹⁷ Strict isolation of suspected cases, aseptic burials of known victims, and quarantine of potential contacts is necessary to decrease the risk of epidemics. No definitive treatment exists, although experimental drugs and vaccines are undergoing testing. Two vaccine candidates, chimpanzee adenovirus serotype 3 (ChAd3-ZEBOV) and recombinant vesicular stomatitis virus (VSV-EBOV), are currently in phase III clinical trials. Several other vaccine candidates are currently in earlier phases of human testing.¹⁸ The experimental drug ZMapp has been administered to a limited number of victims with promising results.¹⁹

Dengue fever**Key points**

- **Dengue fever is a leading cause of morbidity and mortality in the tropics and subtropics**
- **Clinical manifestations vary widely, from asymptomatic infection to dengue hemorrhagic fever**
- **Diagnosis is made clinically followed by viral detection or antibody testing**
- **Treatment is mainly supportive**

Dengue viruses are members of the family Flaviviridae. With an estimated 390 million infections worldwide each year, dengue is the most prevalent mosquito-borne viral disease and a leading cause of illness and death in the tropics and subtropics.^{20,21} Dengue virus complex has 5 serotypes transmitted by the *Aedes* mosquitos, primarily *Aedes aegypti*.²² The fifth serotype was first isolated in October 2013.²³ In the US, sporadic outbreaks with local transmission have occurred in Florida, Hawaii, and along the Texas–Mexico border.²⁴

Clinical manifestations of the disease vary and include asymptomatic infection, mild dengue, classic dengue, and dengue hemorrhagic fever (DHF).^{23,25} About 75% of dengue infections are asymptomatic.²⁴ Mild dengue can mimic any acute febrile illness.²⁶ Classic dengue fever is a febrile viral syndrome of sudden onset, characterized by fever for 2 to 5 days, severe headache, intense myalgia, arthralgia, retro-orbital pain and, sometimes, a diffuse morbilliform rash that may be pruritic and heals with desquamation.²⁷ DHF (Fig 3) is more likely to develop if an individual previously infected with 1 serotype is later infected with a different viral strain. It is seen primarily in children < 15 years of age and is characterized



Fig 1. Ebola. Ecchymoses on the back. (Courtesy of the Centers for Disease Control and Prevention.)



Fig 2. Ebola. Ecchymoses and petechiae on the foot. (Courtesy of the Centers for Disease Control and Prevention.)

by a more severe course, vomiting, facial flushing, and circumoral cyanosis, as well as weakness.

Preliminary diagnosis is based on clinical features and travel history. Laboratory diagnosis is accomplished by virus detection (viral RNA RT-PCR or NS1 antigen enzyme-linked immunosorbent assay [ELISA]) during the acute phase of the disease and antibody testing (immunoglobulin M [IgM] ELISA and plaque reduction neutralization test [PRNT]) during the convalescent phase.²⁸ A positive tourniquet test is usually present, even with mild clinical symptoms.²⁷

Treatment is nonspecific and supportive. Aspirin and other nonsteroidal antiinflammatory drugs (NSAIDs) should be avoided because of aggravation of hemorrhage. Specific chemotherapies under investigation include interferon and ribavirin.^{27,29} A quadrivalent vaccine was approved recently in Brazil, Mexico, and the Philippines.³⁰

Chikungunya

Key points

- Significant recent increase in travel-associated infections, ongoing epidemic in Latin American and the Caribbean



Fig 3. Dengue hemorrhagic fever. Cutaneous manifestations of dengue hemorrhagic fever in a child.

- Cutaneous manifestations include a variety of mucocutaneous lesions
- Diagnosis is made clinically followed by viral detection or antibody testing
- Treatment is mainly supportive

Chikungunya is an acute febrile illness caused by the Chikungunya virus, of the Togaviridae family, and transmitted by *Aedes* mosquitoes. Chikungunya was first described during an outbreak in southern Tanzania in 1952 and is endemic to many countries in Asia, Africa, Latin America, and the Caribbean. The spread of Chikungunya worldwide has been attributed to a multitude of factors, including mutation of the virus, absence of herd immunity, lack of efficient vector control, globalization, and emergence of another vector, *Aedes albopictus*, in addition to the main vector, *A aegypti*.³¹ Travel-associated cases have been reported in the US since 2006, with a significant increase in 2014 after the first case in the Western Hemisphere in December 2013 and the start of domestic transmission in 2014 (Table II).³²

A variety of mucocutaneous lesions occur in 40% to 50% of cases.³¹ Morbilliform eruption is the most common pattern (Fig 4). Lesions occur most frequently on the upper limbs, followed by the face and trunk, 1 to 5 days after the appearance of fever, and usually subside without sequelae.^{31,35} Excoriated papules caused by itching are often present. Generalized urticaria has also been reported. Hypermelanosis, which is likely postinflammatory, may develop soon after the rash has

Table I. Summary of viral diseases

Virus	Active transmission/ endemic areas	Transmission mechanism	Cutaneous manifestations	Noncutaneous manifestations	Diagnosis	Treatment
Ebola	Guinea, Liberia, and Sierra Leone ^{1*}	Direct contact with bodily fluids	Macules and papules, pinpoint papules first observed around hair roots, and diffuse erythroderma	Flu-like symptoms and hemorrhage	RT-PCR, antigen-capture ELISA, antibody-capture ELISA, and virus isolation	Supportive; avoid NSAIDs
Dengue	Tropics and subtropics	<i>Aedes</i> mosquitoes, primarily <i>Aedes aegypti</i>	Macules and papules	25% of cases are asymptomatic, high fever, severe headache, intense myalgia, arthralgia, retroorbital pain, and hemorrhage (DHF)	Molecular testing if <7 days after symptom onset: RT-PCR (or NS1 antigen ELISA); antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM ELISA and PRNT	Supportive; avoid NSAIDs
Chikungunya	Asia, Africa, Latin America, Caribbean, Florida, Puerto Rico, and the US Virgin Islands	<i>Aedes</i> mosquitoes, primarily <i>Aedes aegypti</i>	Macules and papules	Majority of cases are symptomatic, high fever, and intense debilitating arthralgia	Molecular testing if <7 days after symptom onset: RT-PCR; antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM ELISA and PRNT	Supportive; avoid NSAIDs until dengue ruled out
Zika	South America, Central America, Caribbean, American Samoa, Samoa, Tonga, and Cape Verde ²	<i>Aedes</i> mosquitoes, primarily <i>Aedes aegypti</i>	Macules and papules	20% of cases are symptomatic, mild fever, arthralgia, and conjunctivitis	Molecular testing if <7 days after symptom onset: RT-PCR; antibody testing if ≥4 days after symptom onset or if molecular testing is negative: IgM ELISA and PRNT	Supportive; avoid NSAIDs until dengue ruled out
Trichodysplasia spinulosa	N/A	Unknown	Erythematous follicular papules on central face and protrusion of white-yellowish spicules or keratinous spines from follicular papules	None	Clinical	Restoration of immune competence
Measles	Developing countries, particularly in parts of Africa and Asia	Airborne spread or direct contact with nasal/throat secretions	Pathognomonic Koplik spots and morbilliform eruption	Fever, coryza, cough, and conjunctivitis	Clinical	Supportive
Hand foot and mouth disease	Outbreaks occur around the world; large outbreaks in East Asia and Southeast Asia ³	Airborne spread, contact with feces, contact with nasal/throat secretions, or contact with contaminated objects ⁴	Papulovesicular eruptions with perilesional erythema on the hands and feet, intraoral ulcerations, ^{5,6} and onychomadesis 1-2 months after infection (30% of CVA6 infections) ^{7,8}	Mild fever, sore throat, and loss of appetite ⁹	Clinical and PCR	Supportive

DHF, Dengue hemorrhagic fever; ELISA, enzyme-linked immunosorbent assay; IgM, immunoglobulin M; NSAID, nonsteroidal antiinflammatory drug; PRNT, plaque reduction neutralization test; RT-PCR, reverse transcriptase-polymerase chain reaction.

*In January 2016, the World Health Organization declared the end of Ebola transmission in all West African countries.¹⁰

Table II. Chikungunya in the United States and its territories (local transmission/travel associated)

	2006-2013 ³²	2014 ³³	2015 (As 2015-Nov-10) ³⁴
US	None/28 per year	12 (Florida)/ 2799	None/567
US territories	N/A	4659/51	187/None

resolved.³¹ Xerosis of skin with scaling, desquamation of palms, acute intertrigo-like lesions with penoscrotal or perianal ulceration, aphthous-like ulcers, and lymphedema in an acral distribution have also been noted.^{31,35} While hemorrhage and hemorrhagic skin lesions are more typical of dengue, these have also been reported with less frequency among those with Chikungunya.³⁶ The most characteristic symptom of chikungunya is severe joint pain, which can last for months. Post-Chikungunya rheumatic symptoms >2 years postinfection are common and have been described as either relapsing or persisting in 44% to 79% of cases.³⁷⁻³⁹

Preliminary diagnosis is based on clinical features and travel history. Laboratory diagnosis is accomplished by virus detection (viral RNA RT-PCR) during the acute phase of the disease and antibody testing (IgM ELISA and PRNT) during the convalescent phase.^{28,31,40}

No specific antiviral treatment is available, so it is critical to control the vector. Treatment is nonspecific and supportive.^{35,40} Patients with persisting post-Chikungunya rheumatic syndromes are reported to have responded to NSAIDs, systemic corticosteroids, antimalarials, methotrexate, and biologic antiinflammatory agents.⁴¹⁻⁴³ However, aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage.

Zika

Key points

- Associated with microcephaly birth defects: pregnant women should avoid epidemic areas
- Cutaneous manifestations are nonspecific and similar to dengue and Chikungunya
- Diagnosis is made clinically followed by viral detection or antibody testing
- Treatment is mainly supportive

Zika virus is a member of the family Flaviviridae related to West Nile, dengue, and yellow fever viruses.⁴⁴ From 1951 through 1981, serologic evidence of human infection was reported from African countries and in parts of Asia.⁴⁵ Zika virus is transmitted to humans primarily through *Aedes*

mosquitoes.⁴⁶ The virus can spread from mother to fetus during pregnancy. Spread of the virus through sexual contact has been reported,^{47,48} and viral RNA has been detected in semen 62 days after symptom onset.⁴⁹ Although transmission through blood transfusion has not been reported, it is likely to occur.^{50,51} The virus was also detected in urine.⁵² In 2007, an outbreak estimated at 5005 cases was reported in Yap Island, Micronesia.⁴⁵ Since then, outbreaks have been reported in French Polynesia (2013-2014, estimated at 28,000 cases)⁵³ and most recently in Brazil and other countries in South and Central America.⁵⁴⁻⁵⁷ In December 2015, the first local transmissions of Zika were reported in the Caribbean⁵⁸ and Puerto Rico.⁵⁹ Zika virus transmission has not yet been reported in the US, but hundreds of cases have been reported in returning travelers.⁶⁰ These imported cases, and the fact that the vector is the same as for dengue and Chikungunya, may result in local spread of the virus in some areas of the US.⁶¹ In December 2015, the Pan American Health Organization (PAHO) reported the detection of an unusual increase in microcephaly cases in public and private health care facilities in Brazil. In February 2016, given the recent cluster of microcephaly cases and other neurologic disorders reported in Brazil, following a similar cluster in French Polynesia in 2014, the WHO declared a "public health emergency of international concern."⁶² A retrospective study of the 2013 to 2014 Zika virus outbreak in French Polynesia, using a mathematical model, estimated that the risk of microcephaly was about 1% with infection of the mother with Zika virus during the first trimester of pregnancy. The study could not rule out an increased risk of microcephaly from infection in other trimesters.⁶³ In 2016, the Centers for Disease Control and Prevention (CDC) issued extensive interim guidelines for health care providers caring for pregnant women, women of reproductive age, and for infants and children with possible Zika virus exposure. The CDC also issued guidelines for the prevention of sexual transmission of the virus. The guidelines include the recommendations that pregnant women postpone travel to areas with ongoing Zika virus transmission, providers ask all pregnant women about recent travel history, men who reside in or have traveled to areas of ongoing Zika virus transmission and have a pregnant partner abstain from sexual activity or consistently and correctly use condoms during sex for the duration of the pregnancy, and men who have had a diagnosis of Zika virus disease wait ≥6 months after symptom onset before attempting conception.⁶⁴⁻⁶⁷

About 1 in 5 people infected with Zika virus become symptomatic. Typical findings are fever,



Fig 4. Chikungunya. Morbilliform eruption.



Fig 5. Zika. Palmar desquamation.

rash, arthritis or arthralgia (notably of small joints of hands and feet), and conjunctivitis.^{44–46,52,54,68,69} Cutaneous signs are blanchable macules and papules that start on the face or trunk, 3 to 5 days after the febrile phase, and become more diffuse (Figs 5 and 6).^{46,52} Clinical illness is usually mild, with symptoms lasting for several days to a week. Severe disease requiring hospitalization is uncommon and case fatality is low.⁴⁶ Zika can be difficult to differentiate from dengue and Chikungunya infections. Coinfection with dengue has been recently reported.⁷⁰ Compared with dengue, Zika virus infection has a mild to moderate clinical picture, fever is milder, has more acute onset, and is shorter in duration.⁷¹ Dengue usually presents with more severe muscle pain⁷² and is not typically associated with conjunctivitis. Chikungunya presents with higher fever, more intense joint pain (affecting the hands, feet, knees, and back), and it can disable patients, bending them over so that they cannot walk or perform simple actions.⁷²

Preliminary diagnosis is based on clinical features and travel history. Laboratory diagnosis is accomplished by virus detection (viral RNA RT-PCR) during



Fig 6. Zika. Macules and papules.

the acute phase of the disease and antibody testing (IgM ELISA and PRNT) during the convalescent phase.^{28,52}

No specific antiviral treatment is available, so it is critical to control the vector. Treatment is nonspecific and supportive. Aspirin and other NSAIDs should be avoided until dengue can be ruled out to reduce the risk of hemorrhage.⁴⁶

Trichodysplasia spinulosa

Key points

- Occurs only in immunosuppressed patients
- Cause benign, but significant, facial disfigurement
- Cutaneous manifestations include characteristic follicular papules and keratin spines
- Treatment is mainly supportive

Trichodysplasia spinulosa (TS) is a rare skin disease that occurs almost exclusively in immunosuppressed patients, especially posttransplant patients receiving immunosuppressive therapy. In total, 32 cases have been reported in the US, Netherlands, Australia, Germany, Spain, France, and Canada. TS affects both children and adults. TS was initially thought to be an adverse side effect of cyclosporine, however, reactivation of a TS-associated polyomavirus (TSPyV) infection has recently been causally linked to TS development.

Although TS is considered benign, affected patients can suffer from facial disfigurement. In all reported cases, patients have presented with flesh-colored to erythematous follicular papules on the central face (Fig 7).⁷³ Papular eruption was accompanied by mild pruritus in one-third of cases.⁷⁴ Other gross characteristics include protrusion of white-yellowish spicules or keratinous spines from follicular papules and varying degrees of alopecia, most frequently involving the eyebrows and less frequently affecting the eyelashes and scalp hairs.^{74–76} In addition, facial contours are often



Fig 7. Trichodysplasia spinulosa. Follicular papules. (Courtesy of Michael G. Wilkerson, MD, Department of Dermatology, UTMB, Galveston, TX.)

distorted because of thickening of the skin. While TS lesions are most prominent on the nose, forehead, and ears, eruptions can also occur on the neck, trunk, and extremities.⁷⁷⁻⁸¹

TS can be diagnosed clinically, although its distinct histologic, ultrastructural, and molecular features facilitate definitive diagnosis.

There are limited data available regarding the treatment of TS. Topical cidofovir and oral valganciclovir have shown clinical improvement. The natural history of untreated TS is unclear; however, the condition improves with restoration of immunocompetence. The transformational potential of hyperproliferative TS lesions into malignancy is unknown.^{76,78,82,83}

Measles

Key points

- Measles is highly contagious
- Recent outbreaks were caused by vaccine noncompliance
- Cutaneous manifestations include pathognomonic Koplik spots and a morbilliform eruption
- Treatment is mainly supportive

Measles is a highly contagious childhood infection caused by a virus from the Paramyxoviridae family. Since the development of the measles vaccine in 1967, the incidence of measles has decreased by 99% in the US, but 644 measles cases were reported in the US in 2014—the highest number in the 21st century—because of noncompliance with recommended vaccinations.⁸⁴ A single outbreak in early 2015 resulting from an infected person visiting Disneyland resulted in 125 cases.⁸⁵

Infection is characterized by a prodromal phase of fever, coryza, cough, and conjunctivitis for 3 to 4 days. Cutaneous manifestations include pathognomonic Koplik spots and a morbilliform eruption that

may include both macules and papules. Widespread skin rash is a classic sign of measles. This rash can last up to 7 days and generally appears within the first 3 to 5 days of exposure to the virus. The rash commonly develops at the head and spreads to the trunk to the lower extremities,⁸⁴ although the reverse pattern has been observed in atypical cases.

The diagnosis is made clinically, although serology, cultures, antigen detection, and RT-PCR can be used for confirmation.

Management is largely supportive. The WHO recommends the administration of vitamin A to children with acute measles.⁸⁶ Ribavirin may be beneficial in patients with severe measles, with subacute sclerosing panencephalitis.⁸⁷

Hand foot and mouth disease from enterovirus 71 or Coxsackievirus A6

Key points

- Coxsackievirus A6 is associated with significant morbidity
- Characteristic cutaneous manifestations include sudden papulovesicular eruptions with perilesional erythema on the hands and feet and intraoral ulcerations
- Treatment is mainly supportive

Hand foot and mouth disease (HFMD) is usually a benign febrile illness most commonly caused by Coxsackievirus A16 (CVA16). Most cases involve children <5 years of age⁸⁸ and involve fecal–oral transmission.⁵ Other causative agents include enterovirus 71 (E71), which is the second-most common cause of HFMD, but has recently displayed more severe manifestations involving neurologic sequelae that, in some cases, lead to death.⁸⁹⁻⁹¹ Another causative agent is CVA6, which has been emerging as an increasingly common enteroviral pathogen and is associated with more significant morbidity.⁵

Sudden papulovesicular eruptions with perilesional erythema on the hands and feet and intraoral ulcerations are the typical characteristic appearances of HFMD caused by E71.^{5,6} The vesicles initially contain clear fluid, but turn pustular.⁶ Recently, CVA6-induced HFMD has been reported in both older children and adults (outside of the conventional age range of traditional HFMD) and causes atypical manifestations, which can include onychomadesis 1 to 2 months after infection in approximately 30% of cases.^{7,8} More severe cases of Kaposi varicelliform eruption associated with enteroviral superinfection of patients with atopic dermatitis have been reported in association with CVA6.⁹²

HFMD is usually diagnosed clinically; however, the recent sharp rise in E71 cases presenting with neurologic symptoms—often before HFMD is suspected—limits clinical diagnosis.⁶ CVA6 can have atypical manifestations and may present in both older children and notably in adults, who are often misdiagnosed.⁵ Serologies are insensitive⁷ to identify individual causative agents, but PCR studies of laboratory specimens from stool and blood along with biopsy specimens may aid in the diagnosis.

E71 and CVA6 are more likely to cause a more severe clinical picture than the more common Coxsackie A16 version of HFMD.⁵ Still, a majority of E71 and CVA6 cases are usually self-limiting after 7 to 10 days.^{6,8} Because of the increased prevalence and incidence of case fatalities in HFMD, vaccines are under development.^{9,3} Until then, conservative management with hydration is the standard of care.

EMERGING BACTERIAL DISEASES

Melioidosis

Key points

- Melioidosis is spreading to the Americas
- Cutaneous manifestations include pustules or abscesses
- Diagnosis is by body fluids culture
- Treatment includes intensive supportive care, draining of abscesses, and intravenous antibiotic therapy

Burkholderia pseudomallei, a Gram-negative rod bacterium found in soil and water, is the causative agent of melioidosis. It is primarily transmitted through direct contact with contaminated soil and surface waters.^{94,95} Southeast Asia, south Asia, northern Australia, and southern China are well recognized as the major endemic regions for melioidosis.^{95,96} However, new endemic foci have been reported in multiple regions of Africa and the Americas.^{97,98} Outside of the endemic regions, including the US, most cases are acquired by travelers to these endemic regions and through occupational exposure.⁹⁸⁻¹⁰¹

Noncutaneous manifestations include cough, chest pain, fever, and joint pain.¹⁰² The most common presentation in adults is pneumonia.¹⁰⁰ Cutaneous manifestations are seen in 10% to 25% of patients and include cutaneous pustules or subcutaneous abscesses (Fig 8). The most common cutaneous manifestation in children is acute suppurative parotitis.

Culture of *B pseudomallei* from body fluids is diagnostic.^{95,100}

Treatment of melioidosis is intensive supportive care, draining of abscesses, and antibiotic therapy

initiated with intravenous ceftazidime, imipenem, or meropenem for 10 to 14 days, followed by 20 to 24 weeks of oral trimethoprim-sulfamethoxazole.¹⁰³

Acinetobacter baumannii—associated infection

Key points

- *Acinetobacter baumannii*—associated infection is an emerging nosocomial multidrug-resistant skin infection
- Disease is associated with high mortality rate
- Diagnosis is by bodily fluids culture
- Treat using broad-spectrum antibiotics

Acinetobacter baumannii is a Gram-negative rod bacterium. It is commonly found in soil and water and has the ability to survive on artificial surfaces for extended periods of time—making it an increasingly common cause of multidrug-resistant nosocomial infections¹⁰⁴⁻¹⁰⁶ with the potential to rival MRSA.¹⁰⁷ *A baumannii* refers to a group of 3 bacteria (*A baumannii*, *Acinetobacter nosocomialis*, and *Acinetobacter pitti*), which cause more human infections than other *Acinetobacter* species.¹⁰⁸ Infections with *A baumannii* tend to occur in debilitated patients, mostly in intensive care units.¹⁰⁹ Outbreaks have been traced to common-source contamination, particularly contaminated respiratory therapy and ventilator equipment, to cross-infection by the hands of health care workers who have cared for colonized or infected patients or touched contaminated fomites, and to the occasional health care worker who carries an epidemic strain.¹⁰⁹ Although uncommon, *A baumannii* represents a source of nosocomial skin and soft tissue infection (SSTI) in the setting of war wounds, surgical sites, and burns.^{107,109,110} There have also been reports of community-acquired *A baumannii* SSTIs in healthy patients.¹⁰⁷

It is difficult to determine attributable mortality of *A baumannii* infections independent of patients' severe underlying illnesses.¹¹¹ Nosocomial SSTIs include cellulitis,¹¹⁰ skin abscess,¹¹² and necrotizing fasciitis.^{107,113} Most infections involve a skin break, causing a well demarcated erythematous cellulitis with edema having a peau d'orange appearance (Fig 9).¹¹⁰ The cellulitis then changes to a sandpaper-like appearance, which is caused by numerous vesicles. Evolution to hemorrhagic bullae may then occur.¹¹⁰

Culture of *Acinetobacter* from body fluids is diagnostic.

Hospital disinfection routines must be meticulous.¹⁰⁴ Broad-spectrum carbapenems should be used despite increasing resistance. Polymyxins show the greatest activity and should be included in suspected cases.¹⁰⁸



Fig 8. Melioidosis. Multiple cutaneous abscesses and pustules. (Courtesy of Penvadee Pattanaprichakul, MD, Division of Dermatopathology, Department of Dermatology, Faculty of Medicine Siriraj Hospital, Bangkok, Thailand.)



Fig 9. *Acinetobacter baumannii*-associated infection. Ulcers of the leg.

hematogenously disseminated infection occurs after days or weeks and is characterized by multiple EM lesions; approximately 20% to 50% of patients develop multiple EMs at sites of hematogenous dissemination. Stage 3, a persistent infection, may result in acrodermatitis chronica atrophicans (ACA) months or years later. ACA is associated with *Borrelia afzelii* (only in Europe) and is most common in women >40 years of age. ACA lesions are typically located on the extensor surfaces of the hands and feet, begin insidiously with reddish-violaceous discoloration, and become sclerotic or atrophic over a period of years.

Early Lyme disease is diagnosed clinically in patients with EM in endemic areas. A patient with a characteristic EM lesion will likely be seronegative, because the lesion appears before development of a diagnostic, adaptive immune response. However, in disseminated and late Lyme disease, diagnosis can be made using a 2-tier serologic testing strategy, first by a sensitive ELISA followed by a more specific Western blot test.

Patients with EM should be treated with doxycycline (preferred), amoxicillin, or cefuroxime for 14 to 21 days. Among patients with early disseminated disease and ACA, treatment may be prolonged.

Lyme borreliosis

Key points

- **Lyme borreliosis is a multisystem infectious disease**
- **The characteristic cutaneous manifestation is erythema migrans**
- **Treat using doxycycline**

Lyme borreliosis is a multisystem infectious disease caused by a spirochete, *Borrelia* (*Borrelia burgdorferi* in the US), that is transmitted by the *Ixodes ricinus* tick. A new species causing Lyme borreliosis, *Borrelia mayonii*, was recently discovered in the US.¹¹⁴ It is the most common tick-borne infection in the US and Europe. In the US, the number of confirmed reported cases increased by 49% from 17,029 in 2001 to 25,359 in 2014.^{115,116} The number of annual cases in the US is estimated at 300,000.¹¹⁷

After a tick bite, Lyme disease progresses over 3 stages with distinct cutaneous manifestations. Stage 1, a localized infection involving the characteristic erythema migrans (EM) at the site of inoculation, begins after 3 to 32 days and fades in 2 to 3 weeks; EM occurs in approximately 70% to 80% of patients. EM expands gradually over a period of days reaching between 5 and 30 cm across, often resulting in a target or “bull’s-eye” appearance.¹¹⁸ In stage 2, a

Rickettsial and related diseases

Key points

- **The diagnosis is based on clinical findings and epidemiology followed by serology or polymerase chain reaction studies**
- **Treat with doxycycline**

Diseases caused by Rickettsia and other related organisms are listed in Table III.

Cat flea rickettsiosis. Since its first documentation in humans in 1994, a worldwide distribution of *Rickettsia felis* has been reported.^{119,120} The causative agent for flea-borne spotted fever in cats, *R felis* infections are primarily transmitted by the cat flea,

Table III. Summary of Rickettsial and related diseases

Antigenic group	Disease	Species	Geographic distribution	Cutaneous findings	Characteristic diagnosis	Definitive diagnosis	First-line treatment
Spotted fever	Cat flea rickettsiosis	<i>Rickettsia felis</i>	Europe, North and South America, Africa, and Asia	None	PCR of eschar biopsy and serology	PCR of eschar biopsy and serology	Doxycycline
TIBOLA		<i>Rickettsia slovaca</i>	Southern and Eastern Europe and Asia	Scalp eschar and lymphadenopathy	PCR of eschar biopsy	PCR of eschar biopsy	Doxycycline
RMSF		<i>Rickettsia rickettsii</i>	North, Central, and South America	Blanching macules and petechiae on the palms and soles	Serology and skin biopsy	Serology and skin biopsy	Doxycycline
Typhus fever	Murine typhus	<i>Rickettsia typhi</i>	Tropical and subtropical areas worldwide	None	Serology and PCR	Serology and PCR	Doxycycline
Ehrlichia	Ehrlichiosis	<i>Ehrlichia chaffeensis</i> , <i>Ehrlichia muris</i> , and <i>Ehrlichia ewingii</i>	Common in the US, possibly worldwide	None	PCR and serology in late settings	PCR and serology in late settings	Doxycycline

PCR, Polymerase chain reaction; RMSF, Rocky Mountain spotted fever; TIBOLA, tick-borne lymphadenopathy.

Ctenocephalides felis. The prevalence of *R felis* in flea vectors is approximately 21% to 32%, but can be as high as 90% in South America, which highlights the possibility that it is a more common human infection.^{121,122} *R felis* is likely underreported because of a lack of awareness and laboratory capabilities.

Less than half of infected patients will develop a rash¹²³ (ie, pruritic macules and papules on the chest, abdomen, and lower extremities¹²⁴). The rash is similar to other rickettsioses, typically starting 3 to 5 days after acute fever.¹²⁵ Inoculation site eschar of the flea bite may occur,¹²⁵ which represents localized inflammation and skin necrosis from bacterial entry.¹²⁶

R felis infections are difficult to diagnose because of signs and symptoms similar to other rickettsioses.¹²⁰ With symptoms of fever, headache, and rash indistinguishable from murine typhus and strong antibody cross-reactivity between the 2 rickettsias, many cases of murine typhus are likely misattributed.¹²⁷ Immunofluorescence assay, the reference standard for rickettsial diagnosis, shows cross-reactivity and is insensitive for species identification.¹¹⁹ PCR, preferably from an eschar via a biopsy specimen or swab, or Western blot is necessary to differentiate it from other febrile illnesses.¹²⁸

Prompt empiric treatment with doxycycline is recommended, because this disease can be life-threatening. Management of the local reservoirs, including rodents, dogs, and cats, are important in tackling the spread of *R felis*.¹²²

Tick-borne lymphadenopathy. First described in 1997, tick-borne lymphadenopathy (TIBOLA) is the association of the *Dermacentor* tick vector with scalp eschar and cervical lymphadenopathy.¹²⁹ The condition has been referred to in the literature by alternate names, including scalp eschar and neck lymphadenopathy after tick bite (SENLAT) and *Dermacentor* species-borne necrosis-erythema-lymphadenopathy (DEBONEL). It is predominantly caused by *Rickettsia slovaca*, and less commonly *Rickettsia ryoja* and *Rickettsia raoultii*. TIBOLA is an emerging infectious disease in Europe, and is the second most common rickettsial disease after Mediterranean spotted fever.¹³⁰ TIBOLA has a higher prevalence during colder seasons, which correlates to the higher activity level of its tick vector *Dermacentor marginatus*. Children and women are at higher risk for TIBOLA, and *Dermacentor* ticks prefer to bite on the scalp, possibly because *Dermacentor* ticks usually bite hairy domestic and wild animals and the longer hair of women and children may attract them.¹³¹

Inoculation site erythema similar to EM can occur.¹³² A 0.5 cm to 2.5 cm necrotic eschar

(Fig 10) lasting up to 1 to 2 months then develops at the original tick bite, with regional painful lymphadenopathy.¹³³ If the tick bite is on the scalp, as 90% of cases have been, facial edema can also occur.¹³¹ After eschar healing, 30% of patients experience localized residual alopecia.¹³⁰

Diagnosis is mainly clinical.¹³⁴ Scalp eschar is characteristic of TIBOLA. Systemic symptoms, such as fever, are seen in only a third of patients, which can help distinguish TIBOLA from Mediterranean spotted fever.¹³¹ PCR of the eschar biopsy specimen is necessary for laboratory identification of the rickettsial organism.¹³⁵

As in other rickettsial infections, standard treatment is doxycycline for 7 to 10 days or macrolide therapy with either erythromycin for 7 to 10 days or azithromycin for 5 days.^{131,136} Treatment should be instituted before return of definitive identification.

Rocky Mountain spotted fever. Rocky Mountain spotted fever (RMSF) is a potentially lethal but curable tick-borne disease caused by *Rickettsia rickettsiae* and in the US by the American dog tick (*Dermacentor variabilis*), Rocky Mountain wood tick (*Dermacentor andersoni*), and brown dog tick (*Rhipicephalus sanguineus*).¹³⁷ The incidence of RMSF has been steadily increasing over the years; the incidence ranged from 365 to 831 per year in the 1990s to 1815 to 4470 between 2008 and 2012, as reported to the CDC.¹³⁸ Although RMSF has been reported in most states, 5 states (ie, North Carolina, Oklahoma, Arkansas, Tennessee, and Missouri) account for >60% of RMSF cases. It has become increasingly common in certain areas of Arizona, where 250 cases and 19 fatalities occurred between 2003 and 2012.^{137,139} Some researchers have speculated that increases in tick-borne diseases may be fueled by ecologic or climate changes, and an increase in actual disease is clearly supported by some focal patterns of recent RMSF emergence.^{139,140} However, a detailed analysis of the data suggests that the increase in reported RMSF incidence further involves a complex interplay of physician awareness, diagnostic practices, and reporting policies.¹⁴⁰

In the early phase of illness, most patients have flu-like symptoms. The hallmark cutaneous manifestation is characterized by initially blanching erythematous rash with macules that become petechial over time.¹⁴¹ Rash develops in 88% to 90% of patients within a few days after the fever. It usually appears first on the ankles and wrists and then spreads to the trunk. The rash that appears on the palms and soles is highly characteristic of RMSF.

A presumptive diagnosis is made clinically in the appropriate epidemiologic setting and can later be



Fig 10. Tick-borne lymphadenopathy. Eschar formation in the center of the violaceous erythema.

confirmed using serology and skin biopsy specimens.¹⁴²⁻¹⁴⁴

Empiric therapy should be initiated promptly and ideally within 5 days of symptoms, because a delay is associated with increased mortality.¹⁴⁵ Doxycycline is the first-line treatment for both adults and children.

Ehrlichiosis. The most common human monocytotropic ehrlichiosis (HME) is caused by *Ehrlichia chaffeensis* targeting macrophages and monocytes.¹⁴⁶ *Anaplasma phagocytophilum* is the cause of human granulocytotropic anaplasmosis (HGA), which has similar signs and symptoms.¹⁴⁶ The lone star tick, *Amblyomma americanum*, is the main transmission vector. The number of cases in the US has increased steadily from 200 cases in 2000 to 961 cases in 2008.¹⁴⁷ It is also becoming an emerging disease elsewhere in the world.

Usually presenting 5 days after onset of illness, macular and papular eruptions, as well as petechiae and erythema involving the trunk and extremities, can present in ≤33% of cases with HME. In children it can be as high as 67%.¹⁴⁸ Occasionally, edema, vesicles, and purpuric plaques have been reported.

Infections typically present with flu-like symptoms. Individuals with outdoor lifestyles who present with laboratory abnormalities, such as leukopenia, thrombocytopenia, and transaminitis, should be suspected of recent infection by ehrlichioses. PCR analysis should be performed because serologies can be negative in the acute setting.

Doxycycline for 5 to 14 days is the recommended treatment regimen. Delayed treatment can result in progression to longer hospitalizations, intensive care unit admission, and fatalities.

Other expanding bacterial diseases

Methicillin-resistant *Staphylococcus aureus* (MRSA) has emerged as the most common cause of SSTIs. Although MRSA was largely confined to health care settings, since the mid-1990s the incidence of community-acquired MRSA has steadily increased.¹⁴⁹

The CDC estimates that there were 15,138 cases of CA-MRSA in 2012.¹⁵⁰

Multidrug-resistant tuberculosis (MDR-TB) is yet another infection that is expanding worldwide. The WHO estimated that there were 480,000 cases of MDR-TB in 2014.¹⁵¹ However, prevalence in the US has remained stable since 1997.¹⁵² According to the CDC, there were 91 cases of MDR-TB in 2014.¹⁵³

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Emerging infectious diseases with cutaneous manifestations



Fungal, helminthic, protozoan and ectoparasitic infections

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Learning objectives

After completing this learning activity, the participant should be able to describe the cutaneous manifestations of emerging fungal, helminth, protozoan, and ectoparasite infections and identify appropriate therapy for case studies of emerging fungal, helminth, protozoan, and ectoparasite infections with cutaneous manifestations.

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Given increased international travel, immigration, changing climate conditions, and the increased incidence of iatrogenic immunosuppression, fungal, protozoan, helminthic, and ectoparasitic infections that were once uncommon are being seen more frequently in the Western hemisphere. However, the diagnosis and management of these infections is fraught with a lack of consistency because there is a dearth of dermatology literature on the cutaneous manifestations of these infections. In addition, delays in the diagnosis and treatment of these diseases can lead to significant patient morbidity and mortality. We review the epidemiology, cutaneous manifestations, diagnostic modalities, and treatment options for emerging fungal, protozoan, helminthic, and ectoparasitic infections. It should be noted, however, that throughout this review we cite statistics documenting their increased incidence to back-up these infections as emerging, and although some of the diagnoses are clinical, others rely on newer laboratory tests, and the possibility exists that the increased incidence could be caused by better detection methods. (J Am Acad Dermatol 2016;75:19-30.)

Key words: balamuthia; Chagas disease; cysticercosis; emerging infections; fusariosis; leishmaniasis; myiasis; phaeohyphomycosis; toxocariasis; zygomycosis.

Although many of the fungal, protozoan, helminthic, and ectoparasitic infections we highlight in this article were once thought to primarily affect individuals in developing countries, these infections are also present in the United States

and Europe. Because of increased travel, globalization, immunosuppressive drugs, and immigration from endemic areas, the number of cases is increasing. We highlight some of these emerging diseases with which dermatologists should be

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Abbreviations used:

BAE:	<i>Balamuthia</i> amoebic encephalitis
CD:	Chagas disease
CDC:	Centers for Disease Control and Prevention
CL:	cutaneous leishmaniasis
CT:	computed tomography
ELISA:	enzyme-linked immunosorbent assay
PCR:	polymerase chain reaction
PHM:	phaeohyphomycosis
TES:	<i>Toxocara</i> excretory–secretory

particularly familiar in order to minimize the risk they pose to public health (Table I).

EMERGING FUNGAL INFECTIONS

Zygomycosis

Key points

- Most commonly caused by *Rhizopus* spp
- Increasingly seen in patients who have undergone hematopoietic stem cell transplants
- Presents as necrotic plaques and darkly colored nodules

Zygomycosis is caused by fungi from the genera *Rhizopus* (most common), *Lichtheimia*, and *Mucor*.¹ The spores of these fungi are ubiquitous in nature and can be acquired most commonly by direct inoculation and also from ingestion or inhalation.² Although zygomycosis is rare, the incidence in patients who have undergone hematopoietic stem cell transplants (HSCTs) is increasing. Data from the Transplant-Associated Infection Surveillance Network in the United States shows an increased annual incidence of zygomycosis in HSCT patients from 1.7 per 1000 patients in 2001 to 6.2 per 1000 patients in 2004.³ Similar increases have been noted in Europe, with 1 study in France showing an increase from 0.7 per million in 1997 to 1.2 per million in 2006.⁴

The major risk factors for zygomycosis after HSCT are steroids, diabetes, iron overload, neutropenia, malnutrition, and severe graft-versus-host disease.^{4,5} Prophylaxis with antifungal agents without activity against Zygomycetes, such as voriconazole, is implicated in breakthrough infection.¹ Many infections occur >100 days after HSCT,³ which some hypothesize may be an unintended result of protocol-driven posttransplant antifungal prophylaxis with voriconazole.⁶ Zygomycosis has 5 classic clinical presentations: rhinocerebral, pulmonary, gastrointestinal, disseminated, and cutaneous. The cutaneous manifestations and course of zygomycosis are varied. The disease can have a gradual onset with slow progression or can be fulminant. Cutaneous findings are polymorphous and include dark pink

violaceous or yellow nodules, black discoloration with surrounding edema, tinea corporis-like lesions, targetoid plaques, “fuzzy discharge” at the borders of a wound, gangrene, necrotizing fasciitis, and cutaneous abscesses (Fig 1). Lesions often have a typically rapid evolution to a necrotic eschar caused by vascular invasion and infarction.⁷ The arms and legs are more commonly involved,² and lesions have a predilection for occluded or traumatized locations, such as catheter placement sites.

Cutaneous zygomycosis can be diagnosed via fungal culture, histopathology, and direct observation of characteristic hyphae on microscopy. Testing for Zygomycetes DNA using a polymerase chain reaction (PCR) study is also available. Prompt treatment of zygomycosis, often initiated empirically, is essential. In localized disease, surgical debridement and systemic antifungals are recommended. Disseminated infection has a poor prognosis. Antifungal drugs that are approved for the treatment of zygomycosis are amphotericin B and isavuconazonium sulfate, the latter of which was approved in 2015.

Fusariosis

Key points

- Second most common mold infection in immunocompromised patients
- Presents as erythematous subcutaneous nodules and tender red or gray papules or macules
- Treatment consists of surgical debridement and amphotericin B or voriconazole

Fusariosis causes a broad spectrum of infections in humans, particularly in immunocompromised patients, such as those with hematologic malignancies and in patients who have undergone HSCT. The introduction of fluconazole as standard prophylaxis in the setting of HSCT has led to a decreased incidence of yeast infections in this population, namely *Candida* species, and an increase in mold infections (against which fluconazole has no use). In addition, the increased incidence can also be attributed to increasing numbers of HSCT, solid organ transplantation, and newer and more potent chemotherapeutic agents that have dramatically increased the pool of immunocompromised patients.⁸⁻¹⁰ *Fusarium* spp are now the second most common cause of mold infections, behind only *Aspergillus* spp.⁸ Many authors contend that since the first case in 1973, the incidence of invasive fusariosis has dramatically increased.⁸⁻¹¹ According

Table I. Epidemiology, cutaneous findings, diagnosis, and treatment of emerging fungal, helminthic, protozoan, and ectoparasitic infections

Disease	Organism	Skin findings	Diagnosis	Therapy
Zygomycosis	<i>Rhizopus</i> (most common), <i>Lichtheimia</i> , and <i>Mucor</i>	Pink-violaceous or yellow nodules, black discoloration with edema, targetoid plaques, "fuzzy" discharge, abscess, necrotizing fasciitis, and "tinea corporis"-like lesions	Fungal culture, histopathology, observation of hyphae on microscopy, and PCR	Amphotericin B and isavuconazonium sulfate
Fusariosis	<i>Fusarium solani</i> , <i>F oxysporum</i>	Onychomycosis, intertrigo, tinea pedis, cellulitis (immunocompetent hosts), painful, erythematous to violaceous papules and nodules with central necrosis (immunocompromised hosts)	Blood culture, cultures of nail scrapings, corneal scrapings, and skin biopsy	Not well established; amphotericin B or voriconazole with wound debridement
Phaeohyphomycosis	<i>Alternaria</i> , <i>exophiala</i> , <i>phialophora</i>	Subcutaneous cysts or abscesses, ulcerated plaques, hemorrhagic pustules, necrotic papulonodules, and cellulitis	Histopathologic examination with Fontana-Masson stain and culture	Surgical excision of subcutaneous disease, itraconazole, voriconazole, or posaconazole
Toxocariasis	<i>Toxocara canis</i> , <i>T cati</i>	Chronic urticaria, cutaneous nodules, prurigo, and various forms of eczema	Diagnosis is often clinical, serologic assay (TES-ELISA followed by Western blot)	Mebendazole, albendazole, and diethylcarbamazine (second-line)
Cysticercosis	Larval stage (<i>Cysticercosis cellulosae</i>) of pork tapeworm <i>Taenia solium</i>	Numerous small papulonodules, cysts in subcutaneous tissue, skeletal muscles, or mucous membranes, urticaria from leaking cyst fluid	Radiography, CT, or MRI demonstrating calcified cysts in head or extremities; ELISA, hemagglutination tests, or enzyme-linked immunosorbent assay	Surgical removal of cysts, albendazole, or praziquantel
Mansonelliasis	<i>Mansonella ozzardi</i> in Central and South America and <i>M perstans</i> and <i>M streptocerca</i> in Africa	Angioedema, chronic pruritus with hyperpigmentary changes, and papular eruption	Blood sample stained with Giemsa stain, skin biopsy, and nested PCR assay	Diethylcarbamazine and mebendazole

Continued

Table I. Cont'd

Disease	Organism	Skin findings	Diagnosis	Therapy
Leishmaniasis	New world: <i>Leishmania amazonis</i> , <i>L chagasi</i> , <i>L mexicana</i> , <i>L naiffi</i> , <i>L brasiliensis</i> , and <i>L guyanensis</i> Old World: <i>L major</i> , <i>L infantum</i> , and <i>L tropica</i>	Painless papules, nodules, or ulcers with raised edge and central crater (can have hundreds of lesions in diffuse CL); nodules and infiltration of the nasal cartilage with destruction of the nasal septum in mucocutaneous CL	Slit skin smear with Giemsa stain, culture, and PCR	Lesions may spontaneously heal, pentavalent antimonials (mainstay), liposomal amphotericin, miltefosine, azoles, and topical paromycin
Chagas disease	<i>Trypanosoma cruzi</i>	Unilateral painless bipalpebral edema, conjunctivitis, local lymphadenopathy (thr Romaña sign); periorbital cellulitis, furuncle-like violaceous lesions (chagomas), and panniculitis	Acute Chagas—microscopic examination of anticoagulated fresh blood, buffy coat preparation for motile trypanosomes, blood culture; chronic Chagas—ELISA, indirect hemagglutination, indirect immunofluorescence, direct agglutination (need ≥2 tests to be positive)	Nifurtimox and benznidazole
Balamuthia	<i>Balamuthia mandrillaris</i>	Thin, painless, skin-colored to violaceous plaque	Immunofluorescence/immunoperoxidase staining	Not established, combination of azoles, macrolides, and miltefosine have been tried
Myiasis	Variety of fly species, but most commonly <i>Dermatobia hominis</i> (human botfly), and <i>Cordylobia anthropophaga</i> (tumbu fly)	Boil-like lesions, pruritic papule or papulonodule with central punctum, pruritic, serpentine, raised erythematous lesion resembling cutaneous larva migrans, and suppurating wound with visible larvae	Clinical diagnosis, but ultrasonography or dermoscopy can be helpful	Surgical debridement or oral ivermectin

CL, Cutaneous leishmaniasis; ELISA, enzyme-linked immunosorbent assay; MRI, magnetic resonance imaging; PCR, polymerase chain reaction; TES, *Toxocara* excretory–secretory.



Fig 1. Zygomycosis. Well-defined mass with surface crusting and ulceration. (Reproduced with permission from Mondal AK, Saha A, Seth J, et al. Subcutaneous zygomycosis: a report of one case responding excellently to potassium iodide. Indian J Dermatol 2015;60:500-2.)

to Giremia et al,¹⁰ a literature search across all 5 continents revealed that half of reported fusariosis cases occurred in the United States. The species most commonly involved include *Fusarium solani*, *Fusarium oxysporum*, and *Fusarium moniliforme*.¹² Typical portals of entry include cutaneous sites, such as burns, trauma, foreign bodies, and the respiratory and gastrointestinal tracts.

The clinical presentation often includes fever, cutaneous lesions, and sinopulmonary infection. Cutaneous findings evolve rapidly over 1 to 5 days and commonly occur on the trunk and extremities. Lesions are often multiple and at various stages of evolution, and typically present as painful erythematous to violaceous papules and nodules (Fig 2). These lesions often become ulcerated and develop a black or grey eschar. Disseminated infection occurs when ≥ 2 noncontiguous sites are involved.¹³ Infection in the immunocompromised population carries a high mortality rate (50-80%), especially if there is associated neutropenia.¹⁴

A diagnosis of fusariosis can be made with histopathology, Gram stain, mycology, blood culture, or serology. Blood cultures are positive in 50% to 70% of cases.¹² Treatment consists of antifungals (eg, amphotericin B, voriconazole, posaconazole, and isavuconazole) and debridement of wounds. Cutaneous findings are often the first manifestation of infection, and careful skin inspection should be routinely performed in all immunocompromised patients.

Phaeohyphomycosis

Key points

- Caused by >100 species of fungi that have melanized, septate dark hyphae

- Presents as a single inflammatory cyst that evolves into diffuse, indurated, and pigmented plaques
- Fontana–Masson stain for melanin is diagnostic

Phaeohyphomycosis (PHM) is characterized by septate dark hyphae, pseudohyphae, and yeasts in tissue samples. The agents of PHM are diverse and have been attributed to >100 species in a variety of clinical syndromes.¹⁵ These fungi tend to be found in moist environments, such as decaying vegetation, wood, and soil, and are more frequent in tropical and subtropical climates. Most individuals are exposed by inhalation and most cases occur in immunocompetent individuals.¹⁵ However, recent literature shows that PHM has been increasingly reported in immunocompromised patients and is considered an emerging mycosis in this population.^{15,16} In this demographic, clinical presentation varies widely but most frequently presents as a single inflammatory cyst on the extremities that may evolve into diffuse, indurated, and pigmented plaques. Subcutaneous nodules, eschars, macules, papules, pustules, ulcers, and cellulitis on the limbs have also been observed (Fig 3).^{17,18}

Diagnosis can be made via microscopy of potassium hydroxide preparation, fungal isolation from culture, and histopathology. Fontana–Masson stain for melanin is diagnostic for PHM, and the serum galactomannan test can be used to help distinguish it from *Aspergillus*. Treatment consists of surgical excision in combination with a systemic azole antifungal (itraconazole being the preferred agent) for ≤ 6 months.¹⁸

EMERGING HELMINTHIC INFECTIONS

Toxocariasis

Key points

- Caused by *Toxocara canis* and *Toxocara cati*
- Acquired through accidental ingestion of eggs in the soil
- Presents as eczema, chronic urticaria, or chronic prurigo

Toxocariasis is a parasitic disease caused by the dog and cat roundworms *Toxocara canis* and *Toxocara cati*, respectively. The disease is endemic throughout the United States, with studies showing that it may be among the most common human parasitic infections.¹⁹⁻²¹ The US Centers for Disease Control and Prevention (CDC) has designated toxocariasis as a neglected parasitic infection in the US and notes that at least 70 people each year are blinded by this disease.²² Human infection occurs

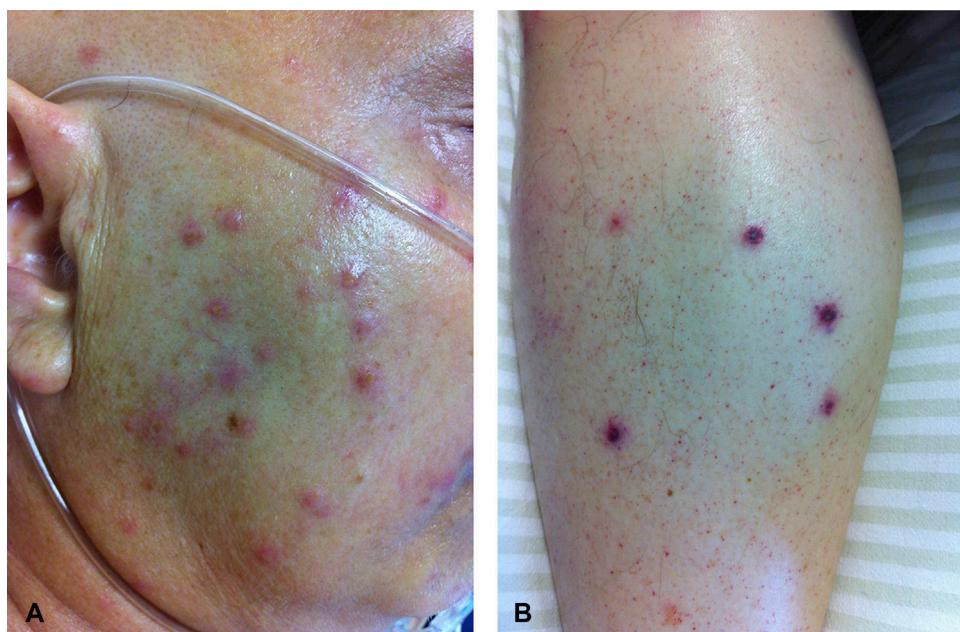


Fig 2. Fusariosis. Papular lesions (**A**) progressed with central ischemia and necrosis (**B**). (Reproduced with permission from Avelino-Silva SI, Ramos JF, Leal FE, et al. Disseminated *Fusarium* infection in autologous stem cell transplant recipient. *Braz J Infect Dis* 2015;19:90-3.)



Fig 3. Phaeohyphomycosis caused by *Alternaria alternata*. Large violaceous reddish indurated plaque with central ulcer on the right knee. (Reproduced with permission from Vermiere SE, de Jong H, Lagrou K, et al. Cutaneous phaeohyphomycosis in renal allograft recipients: report of 2 cases and review of the literature. *Diagn Microbiol Infect Dis* 2010;68:177-80.)

through accidental ingestion of eggs from the environment, commonly in soil contaminated with dog or cat feces. Although a less common route of transmission, humans can also become infected by eating undercooked meat from an animal infected with *Toxocara* larvae. The disease primarily affects children because of their poor hygiene and play habits. It is estimated that millions of Americans have been exposed to the *Toxocara* parasite, with 13.9% of the US population ≥ 6 years of age being seropositive (based on public health data from 1988-1994).¹⁹ Moreover, toxocariasis represents an



Fig 4. Toxocariasis. Chronic urticaria of the dorsal aspects of the hands and thighs. (Reproduced with permission from Gavignet et al.²³)

emerging infection in African Americans and children in the southern US.²¹

Cutaneous manifestations are common and include transient rash, chronic urticaria (Fig 4), various forms of eczema (eg, atopic dermatitis and dyshidrosis), and chronic pruritus or prurigo. Less common but reported skin findings include subcutaneous nodules, vasculitis, and eosinophilic folliculitis. Skin symptoms can sometimes be the only clue to an underlying toxocarial infection. In 2 case control studies carried out in France, 65% of patients with chronic urticaria and 38.1% of patients with chronic prurigo were found to be seropositive for *Toxocara*, respectively. Both of these results were highly statistically significant compared to a dermatologic control group without these 2 traits of interest ($P < .0001$ and .01, respectively). Moreover, appropriate anthelmintic treatment cured the chronic prurigo in 80% of cases and the chronic urticaria in 50% of cases.²³ Clinical laboratory findings include eosinophilia and hypergammaglobulinemia, although these may not be present in patients with chronic infection.²³

Diagnosis is made by detecting toxocarial antibodies directed against *Toxocara* excretory–secretory (TES) antigens using an enzyme-linked immunosorbent assay (ELISA) followed by the Western blot method.^{19,23} Several authors have also suggested lowering the recommended threshold for *Toxocara* diagnosis based on TES-ELISA testing, especially in patients with chronic urticaria, chronic pruritus, and prurigo.²³ Treatment is typically with albendazole (800 mg/day over 5 days) or mebendazole (200-400 mg/day over 5 days).

Cysticercosis

Key points

- Caused by fecal–oral ingestion of *Cysticercus cellulosae*
- Most common cause of seizures worldwide
- Presents as numerous firm, mobile, flesh-colored papulonodules

Cysticercosis, which is common in developing countries, is increasing in the US because of increased travel and immigration from endemic areas.²⁴ The CDC classifies cysticercosis as a neglected parasitic infection in the US and notes that >1000 people are hospitalized with neurocysticercosis each year.²² Cysticercosis is caused by *Cysticercus cellulosae*, the larval form of *Toxocara solium*.

Commonly involved sites in cysticercosis include subcutaneous tissue, the central nervous system (CNS), and skeletal muscle. Cysticercosis is the most common cause of seizures worldwide, and CNS involvement portends a mortality rate of $>50\%$



Fig 5. Cysticercosis. Multiple papulonodules in a patient with cysticercosis. (Reproduced with permission from Khandpur S, Kothiwala SK, Basnet B, et al. Extensive disseminated cysticercosis. Indian J Dermatol Venereol Leprol 2014;80:137-40.)

if the disease is untreated.²⁴⁻²⁶ Neurocysticercosis can be asymptomatic in $\leq 50\%$ of patients, and therefore recognizing the cutaneous manifestations is of vital importance. Cutaneous lesions are characterized by multiple, mobile, firm, papulonodules (average size, 1-2 cm) with normal overlying skin (Fig 5). Lesions are more often palpable than visible, and the number can vary from a few to >1000 . The trunk is the most common location, and subcutaneous involvement occurs in about 54% of cases and may often be the only clinical sign of infection.^{25,26}

Diagnosis is made by obtaining an excisional biopsy specimen of a nodule that shows the cysticercus. A computed tomography (CT) scan of the head often shows calcifications and space-occupying lesions. A magnetic resonance imaging scan is typically indicated if CT scanning is inconclusive.^{25,27,28} ELISA and hemagglutination tests using cyst vesicular fluid as antigen are 80% to 95% sensitive and specific. Enzyme-linked immunoblot assay is the serologic test of choice, with sensitivity and specificity of 100% and 94%, respectively.²⁸ Treatment is with surgical removal if there are only a few nodules or for nodules causing obstructive symptoms in the brain or spinal cord. Albendazole (15 mg/kg/day) for ≥ 8 days is the drug of choice when there are active cysticerci in the brain. Praziquantel can also be used (50 mg/kg/day) for 15 days but has been shown to be less effective than albendazole.²⁵

Mansonelliasis

Key points

- Filarial disease caused by biting midges or blackflies common in Africa and tropical Americas

- ***Mansonella ozzardi* most common in Central and South America and areas of Mexico adjacent to the US border**
- **Presents with chronic pruritus and hyperpigmentary changes**

Mansonella ozzardi is an emergent New World human filarial parasite that is broadly distributed throughout Central and South America. Locally acquired *M ozzardi* infections have been reported in a diverse range of communities throughout Latin America, spanning from Argentina to areas of Mexico adjacent to the US border.²⁹ Parasite incidence surveys have shown population parasitism levels $\leq 15\%$ in multiple Caribbean islands, Argentina, Bolivia, and numerous geographically diffuse localities within the Brazilian Amazon.³⁰

Together with its African relatives (*Mansonella perstans* and *Mansonella streptocerca*), *M ozzardi* is 1 of 3 etiologic agents that causes human mansoneliasis.³⁰ During a blood meal, an infected midge (genus *Culicoides*) or blackfly (genus *Simulium*) introduces third-stage filarial larvae onto the skin of the human host, where they penetrate into the bite wound. They develop into adults that reside in body cavities, most commonly the peritoneal cavity or pleural cavity, but also occasionally in the pericardium (*M perstans*), subcutaneous tissue (*M ozzardi*), or dermis (*M streptocerca*). Skin manifestations associated with angioedema, pruritus, fever, headaches, arthralgias, and neurologic manifestations are quite common for patients with *M perstans*. *M streptocerca* can manifest on the skin via pruritus, papular eruptions, and pigmentation changes, while *M ozzardi* is related to chronic pruritus with hyperpigmentary changes on the skin (Fig 6) and ocular lesions.^{29,30}

Blood samples stained with Giemsa stain will allow identification of microfilariae of *M perstans* and *M ozzardi*.²⁹ Examination of skin biopsy specimens will identify microfilariae of *M streptocerca* that is morphologically very similar to *Oncocerca volvulus*, related to blindness but almost eradicated from the American continent. In addition, a nested PCR assay can be useful to differentiate the skin-dwelling filariae *M streptocerca* from *O volvulus*.³⁰ The most common treatment is diethylcarbamazine, but other drugs have been tried, such as praziquantel, ivermectin, and albendazole, but none has proven to be reliably and rapidly effective. Mebendazole appeared more active than diethylcarbamazine in eliminating the infection, and had comparable overall responses.²⁹



Fig 6. Mansoneliasis. Dermatitis and pigmentation changes caused by *Mansonella ozzardi* infection.

EMERGING PROTOZOAN INFECTIONS

Cutaneous leishmaniasis

Key points

- **Indigenous cases have been reported in the US**
- **There are 3 forms of leishmaniasis with cutaneous manifestations: cutaneous leishmaniasis, diffuse cutaneous leishmaniasis, and mucocutaneous cutaneous leishmaniasis**
- **The mainstays of therapy are pentavalent antimonials**

New World leishmaniasis is endemic from Texas to South America and is caused by *Leishmania amazonensis*, *Leishmania chagasi*, *Leishmania mexicana*, *Leishmania naiffi*, *Leishmania braziliensis*, and *Leishmania guyanensis*. Old World leishmaniasis is primarily endemic in Afghanistan, Algeria, Brazil, Iran, Peru, Saudi Arabia, and Syria and is caused by *Leishmania major*, *Leishmania infantum*, and *Leishmania tropica*.³¹ Both diseases are transmitted when the infected sandfly bites the host. The prevalence of leishmaniasis is 2 million cases worldwide. The US has seen an increase in imported leishmaniasis caused by increased recreational travel and increased deployment of military and contract workers overseas.³¹ In addition, since 1903, 42 cases of autochthonous human cutaneous leishmaniasis (CL) have also been reported in the US. Forty of these cases have been in Texas and 2 in Oklahoma.³²

There are 3 subtypes of leishmaniasis that have cutaneous manifestations: CL, diffuse CL, and mucocutaneous leishmaniasis. CL, the most common form, presents as painless papules, nodules, or ulcers with a raised edge and central crater.³⁰ These lesions typically present on the face, neck, and limbs (Fig 7). Diffuse CL (more common with New World leishmaniasis) can result in >20 to hundreds of cutaneous lesions. Mucocutaneous CL (rare in Old World leishmaniasis) occurs because of lymphatic or



Fig 7. Leishmaniasis. Classic ulcerated crater with raised border at the left arm.

hematogenous dissemination to the upper respiratory tract or oral mucosa from the cutaneous lesion. In this form, nodules and infiltration of the nasal cartilage commonly occur, which leads to destruction of the nasal septum and gross disfigurement.³³

Diagnosis of leishmaniasis can be made by obtaining a slit skin smear of a cutaneous lesion, staining it with Giemsa stain, and examining it under light microscopy. Culture is needed to deduce the species, but the parasite may take ≥ 3 weeks to grow. PCR provides rapid and sensitive testing, but it is not available everywhere.³⁴ Cutaneous lesions of Old World leishmaniasis, and less commonly, New World leishmaniasis can spontaneously heal over months to years. Prompt treatment is necessary for patients in the following situations: ≥ 3 lesions, lesions >2.5 cm, lesions on the face, hands, feet, or over joints, and lesions in immunocompromised patients. Pentavalent antimonials (ie, sodium stibogluconate and meglumine antimoniate) are the mainstay of therapy. However, therapy with these agents is often complicated by adverse reactions and relapses.³¹ Alternatives to pentavalent antimonials include liposomal amphotericin³⁵ and miltefosine, a broad-spectrum alkylly-sophospholipid analogue with activity against promastigote and amastigote stages of *Leishmania* organisms.³⁶ Azole agents, such as ketoconazole and fluconazole, have also been reported to be efficacious.³⁶ Topical paromycin ointment is an alternative for Old World leishmaniasis.³⁴

Chagas disease

Key points

- Acute infection is typically asymptomatic
- May see a local furuncle-like violaceous lesion (chagoma)
- Unilateral periorbital swelling (the Romaña sign) can occur
- Chronic infection may lead to cardiac and gastrointestinal symptoms

American trypanosomiasis, also known as Chagas disease (CD), is caused by *Trypanosoma cruzi*. The disease is transmitted to humans by triatomine insects (blood-sucking bug of the Reduviidae family). These insects deposit their feces, which are laden with *T cruzi*, at the time of biting. However, CD can also be transmitted via mother-to-child transmission,³⁷ food-borne transmission, and blood transfusion. Screening of the US blood supply for Chagas disease began in early 2007.

CD infects approximately 12 million people and kills about 60,000 people yearly.³⁷ In some preliminary estimates, Mexico ranks third and the US ranks seventh in terms of the number of infected individuals with CD.^{37,38} In the US, there are believed to be approximately 300,000 cases,³⁷ although 1 alternative estimate reports $>250,000$ cases in Texas alone³⁹ and ≤ 1 million cases nationwide. In addition, CD is a leading cause of heart disease among people living in extreme poverty in the Western Hemisphere, especially in Latin America.

The majority of the infected individuals remain asymptomatic. Acute CD is most commonly seen in children. The Romaña sign, also referred to as the ophthalmoganglionar complex, develops rapidly, and is characterized by unilateral painless bipalpebral edema, conjunctivitis, inflammation of the lacrimal glands, and local lymphadenopathy. Periorbital cellulitis and metastatic chagomas, sometimes with the presence of fatty tissue necrosis, can also be seen.^{38,40} Chagomas (cutaneous adenopathy complex) are furuncle-like violaceous lesions that are accompanied by regional adenopathy, induration, and discrete central edema. These lesions correspond to the site of parasite entry. Panniculitis, presenting as erythematous edematous plaques, can also occur (Fig 8).

The chronic stage of CD is characterized by manifestations of cardiac and esophageal or colon disease. Sudden death caused by thromboembolic accidents, cardiac conduction delays, or chronic heart failure may occur.^{38,40} Megacolon and megaesophagus and obstruction and perforation of the intestine can occur.

In the acute stage, direct microscopic examination of anticoagulated fresh blood or a buffy coat preparation for motile trypanosomes is indicated. Blood can also be cultured on Novy-MacNeal-Nicolle medium.⁴⁰ The diagnosis of chronic CD is difficult because it relies upon excluding other causes of cardiac or gastrointestinal disease and the presence of antibodies to *T cruzi*. The main serologic tests for *T cruzi* infection are indirect hemagglutination, indirect immunofluorescence, immunoenzymatic (ELISA), direct agglutination



Fig 8. Chagasic panniculitis. Erythematous, warm, edematous subcutaneous plaques affecting the left leg. (Courtesy of Dr Ricardo Romiti, University of São Paulo, São Paulo, Brazil.)

with 2ME, and complement fixation (ie, the Guerreiro–Machado reaction). A positive reaction in ≥ 2 of the mentioned tests allows the physician to confirm chagasic etiology.^{41,42}

There are 2 drugs being currently used for CD: nifurtimox and benznidazole. Both are active against blood and tissue trypanosomes and should be administered for a period of ≥ 30 and ≤ 90 days of treatment. They are contraindicated in pregnancy.⁴³ Recently, a new molecule, Tc24, was identified as a promising antigen in the development of an effective CD vaccine.

Balamuthia

Key points

- Causes a severe and fatal form of encephalitis
- Most commonly seen in children and Hispanic men
- Presents as a thin, painless, skin-colored to violaceous plaque

Since the link between *Balamuthia mandrillaris*, a free-living ameba, and *Balamuthia* amoebic encephalitis (BAE) was elucidated, >200 cases have been reported worldwide. Many experts believe this number is an underestimate because diagnosis of this infection is challenging given lack of standard diagnostic tests and general unfamiliarity with this disease.⁴⁴ The majority of cases are in North America (primarily in the southwest US) and South America. In South America, Peru is a hot spot with 55 cases reported since 1975. Of note, in the US there have been 2 clusters of BAE acquired via organ transplantation; this infection has been added to the list of agents of encephalitis that can be transmitted via organ transplantation.⁴⁵ This entity is of importance not only because it is an emerging



Fig 9. Balamuthia. Painless, skin-colored to violaceous plaque on the central face. (Courtesy of Dr Francisco Bravo, Instituto de Medicina Tropical Alexander von Humboldt and Universidad Peruana Cayetano Heredia, Lima, Peru.)

infection but also given its fatal course if untreated and the universal delay in diagnosis thus far.

B mandrillaris is acquired through a break in the skin or via inhalation and subsequently spreads hematogenously to the brain. The majority of cases appear in children and young Hispanic men.⁴⁴ Both immunocompromised and immunocompetent patients are affected. Cutaneous findings are almost universally seen in the Peruvian cases and often precede encephalitis by weeks to months. Skin findings are less frequently seen in cases from other regions.⁴⁶ The classic cutaneous manifestation is a thin, painless, skin-colored to violaceous plaque that is 1 cm to several centimeters in diameter (Fig 9). The most common location for this plaque is the central face, knee, chest, and elbow. Satellite lesions and ulceration may occur.⁴⁵

The diagnosis of BAE is challenging given the lack of clinical suspicion (because this is a rare disease) and the widespread unavailability of diagnostic tests. Neuroimaging findings are nonspecific. The most precise methods of diagnosis are immunofluorescence/immunoperoxidase staining to detect ameba in skin and brain tissue and detection of *B mandrillaris* DNA via PCR. However, these tests are only available in a few research centers, such as the CDC.⁴⁴ To date, there have only been 10 BAE survivors. Nine of these 10 survivors received a



Fig 10. Myiasis/Furuncular-like nodules on the right posterior shoulder caused by *Dermatobia hominis*. (Reproduced with permission from McGraw and Turansky.⁵²)

combination of azoles, macrolides, and miltefosine ranging from a few months to >5 years.^{44,47}

EMERGING ECTOPARASITIC INFECTION

Myiasis

Key points

- Caused by infestation of humans by larvae from the order Diptera
- Three cutaneous forms of disease: furuncular, migratory, and wound
- Typically self-limited

Myiasis is an infestation of live human and vertebrate animals by larvae (maggots) of a variety of fly species of the order Diptera. Although relatively rare in developed countries, an increased incidence of myiasis has been noted in nonendemic countries.^{48,49} This has been attributed to increased international travel, ecotourism, and increased immigration from endemic regions. Several studies have shown myiasis to be 1 of the 5 most common dermatologic conditions acquired while traveling, representing 6% to 11% of cases.^{50,51} However, cases of myiasis in individuals from nonendemic regions of North America without a significant travel history have also been reported.⁴⁹

Cutaneous myiasis presents in 1 of 3 ways: furuncular, migratory, or wound, depending on the infesting larvae. Furuncular myiasis is most commonly caused by *Dermatobia hominis* (the human botfly) and *Cordylobia anthropophaga* (the tumbu fly). Furuncular myiasis presents as a pruritic, erythematous papule at the site of the bite. Later, this papule develops into a furuncle-like nodule with a central pore (Fig 10). Wound myiasis is most commonly caused by *Cochliomyia hominivorax* and *Chrysomya bezziana*. Fever, chills, pain, bleeding from the infection site, leukocytosis, and eosinophilia may be seen. If infestation occurs around orifices of the head, the larvae have been

known to burrow into nasal bones, eyes, or brain tissue, causing sepsis, blindness, and death.⁵² Creeping or migratory myiasis is most commonly caused by *Hypoderma bovis* or *Gasterophilus intestinalis* and is generally seen in those working or living near cattle and horses. This form presents as an intensely pruritic, serpentine, and raised erythematous lesion resembling cutaneous larva migrans.⁴⁸

Myiasis infections are typically self-limited, with minimal morbidity. The diagnosis is typically made based on clinical symptoms and exposure history. Ultrasonography and dermoscopy can also aid in the diagnosis.⁵³ Treatment options include oral ivermectin, surgical removal or debridement under local anesthesia, and occlusion of the central punctum for several hours.^{52,53}

In conclusion, emerging infections that pose a risk to public health have been highlighted in an effort to increase awareness and improve patient outcomes. The recognition of early cutaneous signs in these diseases is important, because some of these diseases only have cutaneous manifestations or the cutaneous signs precede systemic illness. Of note, the CDC offers PCR testing for many of these emerging infections. Specimens can be submitted directly to the CDC from state public health laboratories or federal health agencies. Specimens from private institutions need to first be submitted to the local state health laboratory.⁵⁴ By investigating suspicious lesions early in immunosuppressed patients, implementing improved sanitation and hygiene practices, and implementing appropriate therapy in a timely manner, significant reductions in patient morbidity and mortality can be achieved.

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Dermatologic surgery emergencies



Complications caused by occlusion and blood pressure

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Learning objectives

After completing this learning activity, participants should be able to describe the potential emergencies that can result from dermatologic surgery, lasers, and cosmetic surgery and describe methods of diagnosis of each specific type of emergency.

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Editors

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While the overall incidence of emergencies in dermatologic surgery is low, emergent situations can occasionally pose a risk to patients undergoing such procedures. The clinical importance of several types of emergencies related to vascular occlusion, hypertension, and hypotension are reviewed, and relevant epidemiology, clinical manifestations, diagnosis, work-up, management, and prevention are discussed. Early detection of these emergencies can mitigate or forestall associated adverse outcomes, thereby allowing the outstanding record of safety of dermatologic surgery to continue. (J Am Acad Dermatol 2016;75:243-62.)

Key words: complication; dermatologic emergency; embolism; hypertension; hypotension; myocardial infarction; stroke; surgery.

Despite the high level of safety and low adverse event rates associated with office-based dermatologic surgery, emergencies can arise, and it is helpful for dermatologists to be able to identify the onset of these. Timely recognition and appropriate management can minimize detrimental patient outcomes and ensure that dermatologic surgery maintains its privileged position as an unusually safe surgical specialty.

In this review we describe several potentially reversible but serious adverse events that may be

Abbreviations used:

ABC:	airway breathing and circulation
DBP:	diastolic blood pressure
DVT:	deep vein thrombosis
EMS:	emergency medical services
LMWH:	low molecular weight heparin
MMS:	Mohs micrographic surgery
OD:	organ damage
PE:	pulmonary embolism
PFO:	patent foramen ovale
SBP:	systolic blood pressure
VTE:	venous thromboembolism

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encountered during the practice of dermatologic surgery. For each, we provide an explanation of its clinical significance; incidence data, when available; a description of clinical presentation, including signs and symptoms; other specific characteristics or tests that can aid in establishing a diagnosis; treatment and management options, including preventive strategies; and long-term outcomes. The scope of the potential emergencies spans procedures performed commonly by the general dermatology clinician and those performed by more specialized oncologic or cosmetic dermatologic surgeons.

Many of the adverse events and emergencies considered in this review are uncommon or rare. Nonetheless, we include these for completeness. In addition, many of these uncommon problems are by nature unpredictable and idiosyncratic, often associated with few if any steps that a dermatologist can reasonably preemptively implement to avoid their occurrence. Finally, while we generally include a detailed methodology for addressing and managing each adverse event, the portion of such management that is performed by the dermatologist is limited. In many and likely most situations, the dermatologist's role is merely to identify that something is wrong, and then to make a referral to another specialist. A simplified description of what may be done by nondermatologists is included to help the dermatologist refer to the correct service and communicate with the doctor receiving the referral, and not because the dermatologist is responsible for further management.

The first part of this review will address complications that may be seen after a range of dermatologic interventions, specifically those related to vascular occlusion and changes in blood pressure. The second article in this series will consider complications more likely to occur as a result of systemic reactions, trauma, and high-energy sources.

AIR EMBOLISM

Key points

- **Air embolism can present as a complication of foam sclerotherapy, but rarely results in significant permanent deficits**
- **Two reports of air emboli as a complication of Mohs micrographic surgery have also been described, both involving extirpation of large scalp tumors with calvarial invasion**
- **Factors that may create an increased risk for a symptomatic event include patent foramen ovale and sclerotherapy foam characteristics**
- **Cerebral vessel spasm has been suggested as an alternative mechanism of transient neurologic deficits after sclerotherapy**

- **Air emboli may be asymptomatic or may present with a range of symptoms, depending on where the blockage occurs**
- **The management of clinically significant air emboli relies on restoring flow to the cardiopulmonary circulation and promoting the reabsorption of intravascular air**

General/incidence

Air embolism can occur as a complication of foam sclerotherapy and presents with clinical manifestations ranging from asymptomatic to pulmonary or neurologic events.^{1,2} The median incidence of symptomatic neurologic events after foam sclerotherapy (including scotoma and migraine) is estimated to be between 0.3% and 6% for visual disturbances and between 0% and 23% for headaches.³ Reports also have described uncommon but significant neurologic events, including cerebrovascular accident, seizures, and transient ischemic attacks.^{4,5} Air emboli as a complication of oncologic surgery have also been described in 2 case reports.⁶ Both cases involved large and complicated tumors on the scalp and required extension of Mohs micrographic surgery (MMS) to the level of the calvarium.

Risk factors

Factors that may create an increased risk for symptomatic air emboli have been well described. These include patent foramen ovale (PFO), and when foam sclerotherapy is used, specific foam characteristics, such as the type and amount.⁷⁻⁹ Although only 2 case reports of air emboli resulting from MMS have been described, both patients had tumors that extended to the bony calvarium (Fig 1) and were treated in a seated position, potentially contributing to the introduction of air into the circulation.⁶

A PFO—an anomalous connection between the venous and arterial blood supplies—is present in 10% to 27% of the population. PFOs permit the air introduced into circulation (spontaneously or from foam used during sclerotherapy) to rise as far as the right atrium, with the potential for subsequent cerebrovascular gas embolization.^{10,11} An analysis of 3259 patients who underwent ultrasonography-guided foam sclerotherapy for the treatment of varicose veins (ie, the great saphenous vein, small saphenous vein, and small veins) revealed an association between PFO and adverse events that included visual disturbances, migraines, and chest discomfort.⁸ The adverse event rate was low, however, with only 7 patients (0.21%) reporting such events, all of which were temporary, lasting



Fig 1. Cerebral air embolism during Mohs micrographic surgery. The calvarium was intact and appeared clinically normal. Reproduced with permission from Goldman et al.⁶

<2 weeks.¹² Likewise, while an increased amount of injected foam appears to be a risk factor for the development of transient neurologic deficits, specific volumes associated with increased risk have not been determined because of the low incidence of these events. Although some believe that foam ascension and air embolism is the pathomechanism for this phenomenon, reports of transient neurologic deficits (such as scintillating scotoma) after liquid sclerotherapy has led to the support an alternative hypothesis—that of cerebral vessel spasm.⁷ Further contributing to this theory, patients prone to complaints of scintillating scotoma after sclerotherapy are those with a history of migraines, in whom vessels are particularly sensitive.¹ The specific type of sclerosant used may also play a role in the development of symptomatic air emboli.⁹ Polidocanol produces a microfoam with a highly controlled and limited bubble size distribution, which may help to minimize its potential to induce symptomatic gas emboli.¹³ In a study of patients undergoing lower-extremity polidocanol sclerotherapy, 57 of 82 patients were found to have middle cerebral arterial gas emboli by transcranial Doppler monitoring, but none developed neurologic abnormalities or had any evidence of new brain lesions or evidence of cardiac infarction as verified by magnetic resonance imaging

scans and cardiac markers.¹⁴ Therefore, although cerebral air embolism is associated with polidocanol sclerotherapy, the clinical implications of this are generally minimal. Neurologic symptoms, if present, tend to be transient and not usually associated with any long-term cerebral injury.⁹

Pathophysiology

Morbidity caused by vascular air embolism is in part determined by factors related to the volume of air that has entered the vascular system and the rate of accumulation. Patient variables that influence these factors include patient positioning and the height of the bubble within the vasculature relative to the right side of the heart.¹⁵

Small amounts of air introduced into the venous circulation fail to result in clinically symptomatic air embolism.^{16,17} Small bubbles are absorbed into the blood stream before the blood enters the pulmonary circulation, which can also handle relatively large volumes of air. It has been estimated that it would be necessary to put 480 mL of air into the venous system within 20 to 30 seconds to cause death in a person weighing 60 kg.^{17,18} This quantity far exceeds the amount of air likely to be introduced during foam sclerotherapy, and importantly, no reports of mortality related to air embolism after sclerotherapy have ever been described.

The exact mechanism whereby foam sclerotherapy leads to air embolism is unclear, but it has been hypothesized that it is related to the nature of the foam, which is a mixture of gas (ie, air or carbon dioxide) and liquid sclerosant that has become a colloid. Injected foam reverts back to its constituent parts and causes bubbles to accumulate within the vessels.¹⁷ Eckmann et al¹⁹ found that increasingly persistent and larger bubbles are created when air is used as the gas.

Regarding air embolism during MMS, given the small number of reports, the etiology and degree of risk remain to be fully elucidated. In 1 case, air embolus may have resulted from tumor extension into the outer table of bone, which may have exposed small connections to the diploic plexus of veins after the periosteum was removed (Fig 2). In the second case, embolus may have had a similar cause, or may have been caused by the patient's remote history of calvarial manipulation, which caused anatomic changes that predisposed him to air passage into the central venous drainage system.

Clinical features

Air emboli may be asymptomatic or may present with a range of symptoms depending on where the blockage occurs.¹¹ Symptoms are different in those

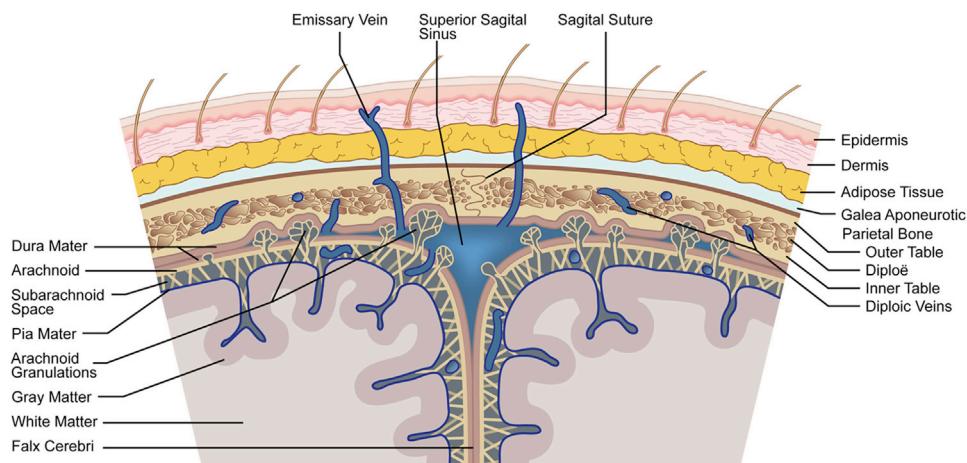


Fig 2. Illustration of cross-section of the scalp. Noncollapsible emissary veins traverse the calvarium to drain into deeper venous structures. These veins can possibly be exposed during extensive surgery on the scalp after removal of the galea, allowing air into the cerebral venous circulation.

who do and do not have a PFO. Those who do not have a PFO may present with pulmonary complaints, such as chest tightness, which is related to pulmonary gas embolism because the gas stays in the pulmonary circulation.^{13,20} Conversely, patients with a PFO may present with neurologic deficits, such as motor weakness or visual disturbances, that are caused by paradoxical cerebrovascular embolization through the PFO.^{11,13}

Diagnosis/imaging tests

Regardless of presentation, clinically significant symptoms after foam sclerotherapy should prompt a work-up for air emboli, which may be difficult to diagnose.²⁰ Referral is made for further evaluation and management to appropriate services, like emergency medicine or neurosurgery. Detection of air embolism can be made with echocardiographic or ultrasonographic evidence of gas bubbles in the heart. Cerebral arterial gas emboli can be detected with transcranial Doppler monitoring or seen on a computed tomography (CT) scan of the head (Fig 3).^{11,21} Other methods of detection, such as end-tidal nitrogen, end-tidal carbon dioxide, pulse oximetry, and even a stethoscope (looking for a characteristic mill wheel murmur) may also be of some diagnostic use.¹⁵ Transesophageal echocardiography can detect macroemboli, microemboli, and paradoxical emboli, but it is expensive and invasive.¹⁵ Precordial ultrasonography, a noninvasive method for detecting air emboli, may be impractical in obese patients because positioning the probe can be difficult.¹⁵ This work-up is outside the scope of routine dermatologic practice, and therefore referral to experts capable of such assessment (eg,

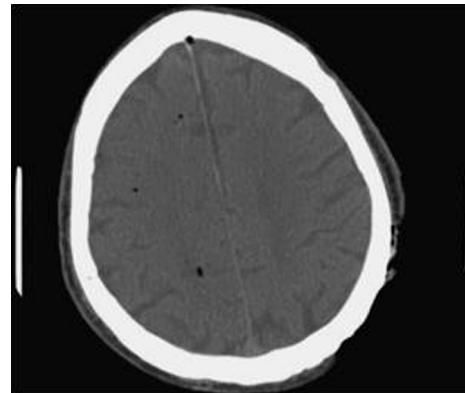


Fig 3. A computed tomography scan reveals air (dark circles) within vascular structures in the brain parenchyma (from patient shown in Fig 2). Reproduced with permission from Goldman et al.⁶

cardiology, emergency medicine, or pulmonology, etc) may be appropriate.

The clinical relevance of detection of air emboli in the absence of symptomatology is debatable. In some samples, all individuals injected with foamed sclerosant have been found to have echocardiographic evidence of gas bubbles within the right heart chambers, and occasionally within the left heart.^{2,21} In a study by Ceulen et al,² patients undergoing foam sclerotherapy were monitored using echocardiography and all patients showed evidence of microemboli, including 5 patients with a PFO. None of these patients experienced symptoms, suggesting that small microemboli are common during foamed sclerotherapy and are inconsequential clinically.² An echocardiographic study of intracardiac bubbles found that gas emboli routinely appeared in the right atrium within 2 to 3 minutes and lasted for

≤32 minutes after injection with sclerosant (polidocanol) in a leg vein.²² Air bubbles in the heart have also been seen after endovenous laser ablation, and less commonly after radiofrequency ablation, in patients who have no PFO on echocardiography.¹ Again, these air bubbles are not typically associated with any neurologic symptoms.¹⁰

Prevention

One proposed preventive method for reducing the risk of foam ascension is allowing the patient to rest for a few minutes in the supine position after sclerotherapy.¹ The sitting position is associated with higher risk of air embolism.¹⁵ Low central venous pressure has been associated with an increased incidence of air embolisms, and therefore hydration is important before procedures that may be likely to induce air embolisms, such as foam sclerotherapy.¹⁵ Minimizing the total volume of foam injected may also reduce risk.

During MMS, risks associated with operating on large and complicated scalp tumors, particularly those extending into the bone or requiring bone manipulation, can be minimized by positioning the patient in the recumbent or prone positions. Such orientations can reduce the risk of air embolus by limiting pressure gradients favoring the influx of air. Exposed bone can be sealed with bone wax and large wounds packed with petrolatum-impregnated gauze, which may further exclude the entry of air.²³

Treatment

The management of air emboli relies on restoring flow to the cardiopulmonary²⁰ circulation and promoting the reabsorption of intravascular air.²⁰ There are conflicting recommendations for treatment, but the role of the dermatologist is not to select between these but rather to make timely referrals to appropriate medical or surgical services. Interventions that have been described include instituting high flow oxygen or hyperbaric oxygen, placing patients in the partial left lateral decubitus or Trendelenburg positions, and aspirating air if a high volume embolus has occurred.¹⁵ Treatment can vary depending on the severity of the clinical presentation, and is likely not necessary for patients who are asymptomatic or minimally symptomatic.²⁰ Obtaining prompt emergent medical assistance may be necessary in a small minority of selected cases with severe symptomatology.

HYPERTENSIVE CRISIS

Key points

- Hypertensive emergencies are hypertensive urgencies (ie, systolic blood pressure >180 mm Hg and diastolic blood pressure

>120 mm Hg) with impending or progressive organ damage

- The clinical manifestations of hypertensive emergency are directly related to the particular end-organ dysfunction
- It is essential to mobilize the local emergency medical services quickly so that blood pressure may be controlled as soon as possible

General/incidence

Hypertension is a ubiquitous and frequently asymptomatic medical condition that affects >65 million Americans.²⁴ Though essential hypertension, the chronic elevation of blood pressure, may affect surgery because of greater intraoperative bleeding,²⁵ decreased duration of activity of local anesthesia,²⁵ and somewhat greater risk of intraoperative serious adverse events,²⁶ it is usually managed easily during dermatologic surgery. We discuss hypertensive crisis (hypertensive urgency or hypertensive emergency), an acute elevation of blood pressure with potential life-threatening consequences. Hypertensive urgencies are elevations of systolic blood pressure (SBP) and diastolic blood pressure (DBP) >180 mm Hg and >120 mm Hg, respectively, without impending organ damage (OD).^{25,27} Hypertensive emergencies are hypertensive urgencies (SBP >180 mm Hg and DBP >120 mm Hg) with impending or progressive OD, such as hypertensive encephalopathy, cerebral infarction, intracranial hemorrhage, acute left ventricular failure, acute pulmonary edema, aortic dissection, or renal failure.²⁷ An estimated 1% to 2% of patients with hypertension have acute pressure elevations that require urgent medical treatment.²⁴

Risk factors

Hypertensive crisis is associated with treatment nonadherence, medication discontinuation or recent reduction in dosage, and with anxiety; in these instances, organ damage can be avoided through prompt management.²⁷ Illicit drug usage, diseases of the kidneys, collagen vascular disease, complications of pregnancy (eg, eclampsia), and unstable postoperative states can cause hypertensive crises that may be more likely to be associated with OD.^{24,28}

All of the aforementioned may occur in a dermatologic office, but a more pertinent etiology during dermatologic surgery is epinephrine use in local anesthetics. Epinephrine stimulates both α - and β -receptors of the noncoronary blood vessels. Generally, α -adrenergic stimulation induces vasoconstriction. However, β -stimulation associated with epinephrine lowers peripheral

vascular resistance and DBP when injected in low doses subcutaneously. In the presence of nonselective β -adrenergic-blocking agents, such as propranolol, epinephrine may induce an unopposed α -vasoconstriction and severe hypertension with reflex bradycardia. There are case reports in the literature of patients on propranolol who were given subcutaneous epinephrine that caused hypertensive crisis episodes.²⁹ On the other hand, a study of MMS by Dzubow et al³⁰ compared 10 patients receiving propranolol with 10 controls who were not; after intraoperative administration of lidocaine with epinephrine, no hypertensive reactions occurred in either group. Therefore, the risk of epinephrine-induced hypertensive crises in patients taking propranolol may be extremely small in dermatologic procedures that are performed under local anesthesia.

Clinical features

The clinical manifestations of hypertensive emergency are directly related to the particular end-organ dysfunction that has occurred: hypertensive encephalopathy, acute aortic dissection, acute myocardial infarction, pulmonary edema, eclampsia, acute renal failure, acute ischemic stroke, or bleeding.^{28,31} Zampaglione et al³¹ reported that the most frequent presenting signs in patients with hypertensive emergencies were chest pain (27%), dyspnea (22%), neurologic deficits (21%), faintness (10.0%), paraesthesia (8.0%), vomiting (3.0%), and headache (3.0%).^{28,31} No particular blood pressure threshold has been associated with the development of a hypertensive emergency. However, organ dysfunction is uncommon with a DBP <130 mm Hg (except in children and pregnancy).^{31,32} The absolute level of blood pressure may not be as important as the rate of increase. For example, in patients with long-standing hypertension, a SBP of 200 mm Hg or a DBP \leq 150 mm Hg may be well tolerated without the development of hypertensive encephalopathy; in children and pregnant women, encephalopathy may develop with a DBP of only 100 mm Hg.³³

Diagnosis/imaging tests/treatment

In the setting of acute elevation of blood pressure in a dermatologist's office, the most important role for the dermatologist is to quickly mobilize the local emergency medical services (EMS) so that blood pressure may be controlled as quickly as possible within an emergency department.^{34,35} When patients experience any of the symptoms of hypertension, EMS should be activated immediately.

EMS should be mobilized based on patient symptomatology and after considering other relevant patient-specific factors. In patients with

long-standing hypertension who do not have symptoms, the risk of functionally relevant elevated blood pressures may be significantly lower than in a naïve, nonhypertensive patient. In hypertensive patients, a deviation from patient-specific benchmark pressures may be more worrisome than an elevation above standard normal pressure levels, which may be abnormally low in the context of preexisting hypertension. In asymptomatic patients, rechecking an elevated blood pressure may be prudent. Measures that will help ensure an accurate reading include allowing a patient to rest in a chair for 5 minutes with their arm supported at heart level and verifying use of an appropriately sized cuff that encircles \geq 80% of the arm with the artery marker pointing directly at the brachial artery.³³ At times, procedure-related anxiety may lead to elevation of blood pressure above normal limits. In asymptomatic patients, relaxation exercises or the use of an anxiolytic where appropriate may help relieve anxiety and lower blood pressure. Clinical context is important, and as mentioned previously, patients with existing high blood pressure may be easily able to tolerate significant acute elevations in pressure, which may not presage an emergency.

HYPOTENSION

Key points

- Hypotension associated with minor procedures may be frequently caused by vasovagal syncope or orthostatic hypotension
- Many vasovagal risk factors are encountered during dermatologic surgery
- Recovery from vasovagal episodes associated with dermatologic surgery is almost always without incident or sequelae
- Minimizing risk is important in certain at-risk patients
- Treatment includes promptly restoring to a recumbent position, preferably Trendelenburg

General/incidence

Hypotension associated with minor procedures may be frequently caused by vasovagal syncope. The term "pseudoallergy" has been proposed by Fader et al²⁵ to describe this phenomenon because patients may recount an "allergic reaction" to a local anesthetic that caused an acute brief unconsciousness. While a vasovagal episode is transient and typically includes a complete recovery, it can require active management if there is a risk of potential injury associated with a loss of postural integrity, or if consciousness is not spontaneously recovered with reasonable rapidity.³⁶ In oral and maxillofacial surgery under local anesthesia, the incidence of

vasovagal episode has been estimated to be 1 in 160 cases.³⁷ The incidence in dermatologic surgery is likely comparable but has not been separately reported.

While this section will primarily focus on vasovagal hypotension, it is important to note that hypotension can also be caused by orthostatics and medications.^{38,39} In particular, orthostatic hypotension may be encountered in the dermatologic surgery setting because of the prone positioning of most dermatologic surgery procedures. Patients that rapidly sit up after completion of a procedure can become predisposed to a hypotensive event. Strictly speaking, orthostatic hypotension is defined as a reduction in blood pressure by 20/10 within 3 minutes of standing.³⁸

Risk factors

Risk factors associated with vasovagal episodes include lack of food, strong emotional stress, sitting, early mornings, acute pain, fear, the Valsalva maneuver, and the sight of blood during venipuncture, although frequently no source is identified.^{25,40-42} Many of the aforementioned events may occur within the context of dermatologic surgery, and therefore the surgeon should be prepared with knowledge of management of vasovagal episodes.

Clinical features

The clinical features of vasovagal episode may include a characteristic prodrome comprised of anxiety, diaphoresis, nausea, tachypnea, tachycardia, or confusion. The skin tends to become pale and cool. Subsequent vagal-induced bradycardia in the setting of decreased systemic vascular resistance can initiate circulatory collapse.²⁵ It is important to note that brief clonic movements can simulate seizure activity. Blood pressure may initially decrease but is restored with recumbency.²⁵ The symptoms associated with orthostatic hypotension are similar to those of vasovagal, the major difference being that the occurrence of the former is preceded by standing.

Prevention

The prevention of vasovagal syncope is important to minimize potential associated deleterious effects. Placing patients in a supine position when performing minor dermatologic surgery procedures decreases risk.²⁵ Patient anxiety may be mitigated by thorough preoperative assessment and explanation of the procedure. Distraction of the patient or preventing the patient from viewing the procedure by blocking the field of view is prudent for certain susceptible patients. Adequate hydration can be

both treatment and prevention in both vasovagal and orthostatic hypotension because dehydration exacerbates both etiologies.^{43,44} Despite efforts at rehydration, medications may still be needed to decrease the likelihood of a prolonged hypotensive event, especially in patients with a known history. In those with vasovagal hypotension, benzodiazepines may be used for prophylaxis, although selective serotonin reuptake inhibitors and beta-blockers may also be effective.⁴³ Vasovagal events may occur more frequently when the patient misses a meal before the procedure. After any procedure, the patient should slowly sit up and be monitored for a few minutes to mitigate the likelihood of a vasovagal episode.

Treatment

If a patient develops a vasovagal reaction, they should be promptly restored to a recumbent position—preferably the Trendelenburg position.⁴⁵ In addition, application of a cool water wash cloth placed on the forehead with a low power fan directed toward the face may be helpful.²⁵ Some have proposed that crossing legs combined with tensing muscles at the onset of prodromal symptoms can abort vasovagal syncopes.⁴⁶

MYOCARDIAL INFARCTION

Key points

- Myocardial infarction is ubiquitous in the United States and can occur spontaneously during a dermatologic procedure
- Severe retrosternal pain is the classic symptom of myocardial infarction, but it is not present in all cases, particularly in women and patients who are diabetic
- Management of myocardial infarction requires prompt recognition and emergent referral to a hospital
- The management of myocardial infarction may include oxygen, nitroglycerin, and aspirin

General/incidence

Acute coronary syndrome (ACS), an umbrella term for acute myocardial infarction and unstable angina, is a life-threatening condition that is common in the United States.⁴⁷ About 625,000 patients are diagnosed with ACS annually.^{47,48} Prompt diagnosis and treatment offer the greatest potential benefit for myocardial salvage in the first hours of ST-elevation myocardial infarction (STEMI); early, focused management of unstable angina and non–STEMI (NSTEMI) reduces adverse events and improves outcome.⁴⁹ Health care providers, including

Table I. Risk factors for myocardial infarction*

Age
Diabetes
Hyperlipidemia
Hypertension
Metabolic syndrome
Obesity
Smoking

*Data from Antman.⁵⁰

dermatologists, are trained to recognize patients with potential ACS in order to initiate the evaluation, appropriate triage, and management as expeditiously as possible.⁴⁹ Providers may choose to monitor vital signs and be prepared to provide cardiopulmonary resuscitation and defibrillation if needed.⁴⁹

There is a paucity of literature on ACS occurring during dermatologic surgery, but this is not to say some risk does not exist.

Risk factors

Risk factors for ACS are listed in Table I.

Clinical features

Clinical features of ACS include a prodrome of chest discomfort resembling classic angina pectoris, but occurring at rest or with less activity than usual and therefore classifiable as unstable angina.⁵⁰ Other symptoms include pain, which varies in intensity but in most patients is severe and, in some cases, intolerable.⁵⁰ Once it manifests, pain is prolonged, usually retrosternal in location, and often radiates down the ulnar aspect of the left arm.⁵⁰ In some cases, the pain of STEMI may begin in the epigastrium and simulate a variety of abdominal disorders.⁵⁰ Other symptoms include nausea, vomiting, dizziness, feelings of profound weakness, shortness of breath, palpitations, cold perspiration, and a sense of impending doom. Atypical or unusual symptoms are more common in women, the elderly, and patients with diabetes. Such unusual findings include pain that is localized to the jaw or medial arm, pain without associated angor amin (ie, the sense of impending doom), or pain without the classical visceral reflexes of vasoconstriction, sweating, or shortness of breath.⁵¹

Diagnosis/imaging tests

Management of ACS starts immediately after ACS is the presumed diagnosis. Immediate contact with EMS is routine.⁵²

Table II. Risk factors for stroke*

Chronic kidney disease
Diabetes mellitus
Family history and genetics
Heart rhythm disorders
Hyperlipidemia
Hypertension
Older age
Physical inactivity
Race
Smoking

*Data from Go et al⁴⁷ and Dyken.⁵⁸

Management

The management of ACS entails monitoring and supporting the airway, breathing, and circulation (ABCs) while waiting for EMS to arrive.⁵² Once EMS arrives and care is transferred, management may include obtaining vital signs,⁵² being prepared to administer cardiopulmonary resuscitation if the need arises, and use of a defibrillator if necessary.⁵² Oxygen, nitroglycerin, and aspirin are all potential therapies that may be administered by EMS personnel.⁵² Nonenteric aspirin (160-325 mg) may be provided, and the patient chews the aspirin tablet to hasten absorption.^{48,49,53,54} Of note, nitrates in all forms are contraindicated in patients with an initial SBP <90 mm Hg or ≥30 mm Hg below baseline, and in patients with right ventricular infarction.⁵⁵⁻⁵⁷ In addition, nitrates are contraindicated when patients have taken a phosphodiesterase-5 inhibitor within 24 hours (48 hours for tadalafil).⁵⁷ The patient should be transported as expeditiously as possible, ideally to a hospital equipped with a cardiac catheterization laboratory for potential intervention as necessary.

STROKE

Key points

- Stroke has been specifically associated with sclerotherapy, but its high prevalence means it may also occur in the setting of other dermatologic procedures, including excisional surgery
- A patent foramen ovale may predispose to stroke via a paradoxical embolism during a surgical procedure
- Damage to the brain during stroke is a result of oxygen deprivation
- There are many mimickers of stroke; a dermatologist's primary role is prompt recognition and referral to emergency medical services

General/incidence

Stroke remains a significant cause of morbidity and mortality in the United States, affecting approximately 6.8 million Americans ≥ 20 years of age.⁴⁷ Approximately 795,000 people experience a new or recurrent stroke each year.⁴⁷ There are many known risk factors for stroke (Table II).

In the context of dermatologic surgery, reports of paradoxical embolism and stroke after sclerotherapy in the setting of a PFO have been described.^{59,60} In addition, given the high prevalence of stroke among Americans, an intraoperative stroke during other dermatologic procedures is possible. Practitioners may be most helpful to affected patients if they can recognize stroke and initiate the appropriate management.

Pathophysiology

Stroke is the failure of oxygenation to the brain.⁵⁴ The brain is a highly oxygen-dependent organ, and longer durations of oxygen deprivation increase the potential for catastrophic and irreversible damage. The potential etiologies of stroke are various, including vessel blockage leading to ischemia/infarction, or subarachnoid hemorrhage and intracranial hypertension leading to hemorrhage.⁶¹

Clinical features

The clinical features of stroke vary greatly and may include the sudden onset of facial palsy, arm weakness, speech impairment, change in consciousness, ataxia, visual loss, vertigo, headache, nausea, or vomiting.^{25,61} There are many mimickers of stroke, and while dermatologists can be of assistance in distinguishing these, it is most important for the physician to alert EMS rather than narrow the differential. Mimickers of stroke include migraines,⁵⁴ drug toxicity,⁵⁴ reaction to anesthesia infiltration,⁶² psychogenic causes,⁵⁴ and hypoglycemia.⁵⁴

Diagnosis

The dermatologist's role in a patient with potential stroke is the prompt recognition of apparent symptoms followed by contacting the emergency services in place at the surgery center (eg, EMS, emergency department transport, or a rapid response team, etc).²⁵ The therapeutic window for the treatment of acute ischemic stroke is limited.⁵⁴ Intravenous fibrinolytic therapy may be helpful if initiated early, after which it is no longer indicated.

Management

Patients with acute stroke are managed initially by assessing the ABCs of basic life support while awaiting the arrival of EMS and transfer of care.⁶¹

Once EMS arrives, early treatment may include the administration of supplemental oxygen, placement of an intravenous line, or ruling out of hypoglycemia.^{54,61} A thorough medical history is obtained, if possible, and if not already available, with the most important current history elements being the time of symptom onset in order to determine the potential for fibrinolytic treatment.⁵⁴ It should be noted that patients whose initial symptoms resolve before EMS arrives should still be examined in a hospital to understand the underlying cause—for instance, 15% of all strokes are heralded by a transient ischemic attack.²⁵

VASCULAR OCCLUSION

Key points

- Vascular occlusion can occur during soft tissue augmentation procedures or sclerotherapy
- Extravascular tamponade after filler injection, direct intravascular injection of filler, and intraarterial injection of sclerosant may result in vascular occlusion
- Potential high-risk anatomic sites where occlusion-associated skin necrosis is likely to occur include the glabella, the perinasal area, the lower face after filler injection, and the popliteal fossa after sclerotherapy
- Symptoms of impending occlusion and necrosis include white or bluish discoloration, often in conjunction with reticulated erythema, with or without pain, that manifests seconds to hours after injection
- Management is targeted at improving blood flow and dissipating the offending agent

General/incidence

Vascular occlusion can occur during dermatologic surgical procedures. Reported inciting events include tamponade caused by soft tissue augmentation material that engulfs and surrounds a vessel, inadvertent injection of prepackaged injectable filler or autologous fat directly into a vessel lumen, or unanticipated intraarterial injection of sclerosant during sclerotherapy.^{63,64} The incidence of filler injection directly into vessels is low, although likely not as exceedingly rare as suggested by published figures, which are based on voluntary reporting and therefore significantly underestimate risk. Dermatologists should not be reassured into complacency by the exceedingly low reported rates of $<0.001\%$,⁶⁵ based on data from drug adverse effects reporting systems for hyaluronic acid filler-related complications in the United States in 2004, or even lower predicted incidence of 0.0001%, based on a 2012 review.⁶⁶ Accurate incidence data are

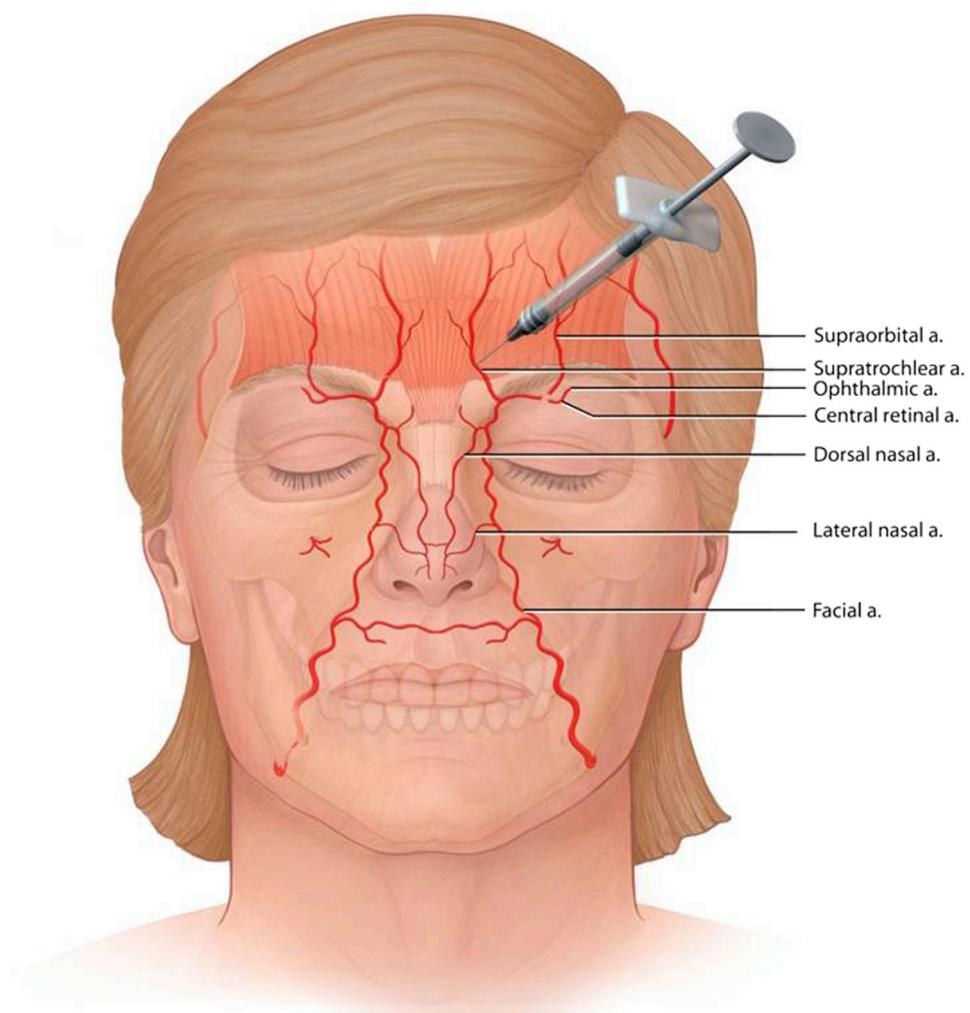


Fig 4. Arteries of the face that may be at risk of occlusion during filler injection procedures. Risk may be minimized by drawing back on the syringe and injecting slowly and relatively superficially while being aware of the vascular anatomy of the face.

difficult to ascertain in the absence of a mandatory, population-based reporting system. The incidence of intravascular occlusion caused by sclerosants is also poorly defined, with 1 published estimate suggesting an incidence of 0.0001%.⁶⁷

Risk factors

Although vascular occlusion events are often idiosyncratic and impossible to prevent, certain procedural and patient characteristics are known to increase risk. Anatomic location is of particular importance. Skin necrosis is more likely to occur in certain potential danger zones proximal to superficial and medium-depth arteries than other areas.⁶⁸ The glabella, central forehead, perinasal area, and lower half of the face (ie, the nasolabial folds and lips) are at higher risk for vascular

compromise because of the proximity of numerous vessels.^{64,66,69-72} Vulnerable vessels include the superior and inferior labial arteries, both branching off the facial artery at the angle of the mouth; the angular artery, the terminal branch of the facial artery at the proximal nasolabial folds; the lateral nasal artery, a branch of the angular artery; the dorsal nasal artery, which anastomoses with the angular artery; the supratrochlear artery, one of the terminal branches of the ophthalmic artery; and the superficial temporal artery, arising from the external carotid artery⁶⁸ (Fig 4). Other vessels that may be at risk include the supraorbital and infraorbital arteries and the facial and transverse facial arteries. The parotid ducts are yet another set of nearby structures with lumens, although only extremely deep injections would potentially impinge on these. Of

note, tissue compromise can occur directly at the injection site and at the site nourished by the compromised vessel.⁶⁶

In addition to vascular compromise, which can lead to skin necrosis, a potentially catastrophic complication of filler injection is retinal artery embolization, with at least 32 cases of iatrogenic retinal artery occlusion reported.⁶⁴ A study of 12 consecutive cases showed that 7 occurred after injection into the glabella, 4 after injection into the nasolabial fold, and 1 after injections into both sites. Autologous fat accounted for 7 of the cases, hyaluronic acid fillers for 4 cases, and collagen for 1.⁶⁴

A review of filler complications reported that hyaluronic acid was the most common filler implicated in necrotic complications, but this is not surprising given that hyaluronic acid fillers are the most widely used in the United States, and there is no reliable evidence that shows any particular filler type is more or less likely to be associated with vascular occlusion.⁶⁶ Knowledge of proper injection techniques and tissue anatomy is a prerequisite for safe injection. Deep injections with high viscosity products into high-risk areas are undertaken with care.⁶⁸ Filler is injected as superficially and slowly as is practicable for the defect in question. Risk of vascular events may be further mitigated by use of low volumes of product in each of several treatment sessions to avoid a large bolus being placed at any single time point.⁷³ Other contributing factors that are considered include anatomic disruptions resulting from scars, trauma, or previous surgery.⁶⁸ Older patients may have more empty space to fill and therefore have a lower risk of compression ischemia, although if large volumes of fillers are injected into such patients, this protective effect may be reduced. Younger patients, especially those with a history of dental or facial surgery, may be at higher risk because of aberrant neovascularization after previous procedures combined with decreased overall tissue laxity.⁶⁸

Intravascular occlusion associated with sclerotherapy also appears to be more frequent at particular anatomic sites. Most notably, the popliteal fossa is at high risk for intraarterial injection of sclerosant because of the proximity of the peroneal artery during injection of sclerosant into the small saphenous vein. Another vulnerable point is the region of the Cockett perforating veins at the retromalleolar ankle area, which is in close proximity to the posterior tibial artery.⁷⁴ Some controversy exists as to the exact etiology of arterial occlusion caused by sclerotherapy. Specifically, it is unclear whether occlusion is more apt to result from direct

intraarterial injection of sclerosant or aberrant communication of the arterial and venous vasculature, which leads to arterial occlusion from retrograde flow after venous injection.⁷⁴ There is a case report of undetected arteriovenous fistula between the anterior accessory saphenous vein and the superficial femoral artery that apparently facilitated arterial embolization of sclerosant with resultant ischemic toe injury.⁶³ The incidence of arteriovenous malformations has been estimated to be 1.2% in the general population.⁶³

Pathophysiology

Skin necrosis as a complication of treatment with injectable fillers is believed to be associated with vascular compromise from arterial or venous obstruction. The occlusion of blood flow can be caused by trauma to the vessel wall, inadvertent intravascular injection of the product, or a direct pressure external tamponade of the filling agent on the vessel causing obstruction of the vessel lumen. In addition, injection-related edema can compromise blood flow by contributing another external force on the vessel wall.⁷⁵

The proposed mechanism of retinal artery occlusion is retrograde flow of filler material⁶⁴ (Fig 4). In the glabella, the occlusion of the retinal or ophthalmic arteries may occur via the supra trochlear or supraorbital arteries. In the nasolabial fold, retrograde flow through the angular and dorsal nasal artery anastomoses may result in embolism to the ophthalmic artery.⁶⁴ Several cases of cerebral infarction have been reported in the setting of retinal artery occlusion. Most reports of cerebral events involve injection of autologous fat, which tends to have a larger particle size than commonly used prepackaged fillers.⁶⁴

Sclerotherapy can be thought of as a controlled thrombophlebitic reaction, and as such, uncontrolled reactions may cause unwanted endothelial destruction.¹⁷ Inadvertent arterial injection or arterial embolization as a result of anatomic vascular variations, such as arteriovenous malformations, can have detrimental consequences, including widespread local tissue ischemia.

Clinical features

Signs of impending occlusion and necrosis include white or bluish discoloration in the context of faint reticulated erythema, with or without pain, that develops seconds to hours after injection.⁶⁴ Immediately after injection, the patient experiences pain and localized blanching of the area, but this may be difficult to distinguish from normal injection discomfort and blanching routinely induced by the

lidocaine solution mixed with the filler. Arterial compromise is more uncomfortable than venous occlusion and is typically heralded by immediate-onset blanching and severe pain that is more obvious than the manifestations of venous occlusion.⁷⁵ The next day or soon thereafter, the presentation of any vascular event becomes more noticeable, with duskeness, ecchymoses, or deep violaceous patches set within a background of reticulated erythema. Left untreated, significant necrosis can ensue; it is desirable to identify vascular occlusion as soon as possible so that proper management can be initiated (Fig 5).^{63,68}

Unfortunately, by the time occlusive events are detected, it is usually at least the day after injection, and much of the associated tissue damage is no longer reversible. When soft tissue loss does occur, in severe cases, skin sloughing, ulceration, and eschar emerge within 3 to 7 days after injection,⁶³ leading to possible hyperpigmentation, textural change, and scarring. Retinal artery embolization presents with sudden unilateral visual loss often with concurrent severe ocular pain in the affected eye.⁶⁴

Diagnosis/imaging tests

The diagnosis of intravascular occlusion is predicated on the recognition of symptoms of occlusion as described above. Knowledge of regional vascular anatomy can aid in recognition because blanching of affected vessels can occasionally be appreciated by a skilled observer. Clinical signs and symptoms of vascular occlusion, including vascular blanching, retiform purpura, painful swelling, and gray to purple discoloration lead to the diagnosis, with imaging studies being of minimal incremental use.

Prevention

Vascular complications are better avoided than treated. Prevention is founded on the judicious use of appropriate injection techniques and the early detection of incipient adverse events so that their impact can be curtailed. Speed of injection is an important variable, with filler ideally injected slowly, using the least amount of pressure feasible. Injection rates <0.3 cc/minute have been hypothesized to be sufficiently low to allow the injectant to dissipate as it flows in and not concentrate in a small space. Low injection pressure may also be effectively counterbalanced by the inherent back pressure in any artery that is pierced, preventing forward flow of filler into the lumen.⁶⁴ Some practitioners recommend aspiration before injection to ensure that the needle tip is not in the vessel; however, given the small caliber of the needle and the viscosity of



Fig 5. Ischemia of the right foot (**A**) with mummification of the toes (**B**) 3 weeks after sclerotherapy in a patient with inadvertent arterial injection and an undetected arteriovenous fistula between the greater saphenous vein and superficial femoral artery. Reproduced with permission.⁶³

most fillers, the absence of a so-called “red flash” cannot be interpreted as definitive evidence that a vessel has not been perforated. Small volume injections placed a few weeks apart can allow a large defect to be corrected without the attendant risks associated with high volume injections. To minimize the likelihood of vascular injury, the use of small-caliber needles has also been advocated. More recently, the use of small bore cannulas has become technically feasible. Cannula tips are blunt, so they do not easily perforate vessels, and the aperture on cannulas is off to the side so that injection force and the forward movement of the cannula are not aligned, but rather are set apart by 90°. Cannulas may be less helpful for some superficial injections, such as those with fillers injected intradermally, or when great precision is required.⁶⁶

During filler injection, extreme pain should be a cause for concern, and should not be dismissed as routine needle discomfort without some investigation of the possibility of vascular injury. Similarly, because signs of vascular occlusion often emerge hours to days after injection, it is important for clinical staff to appreciate the key elements of the clinical presentation and respond speedily and

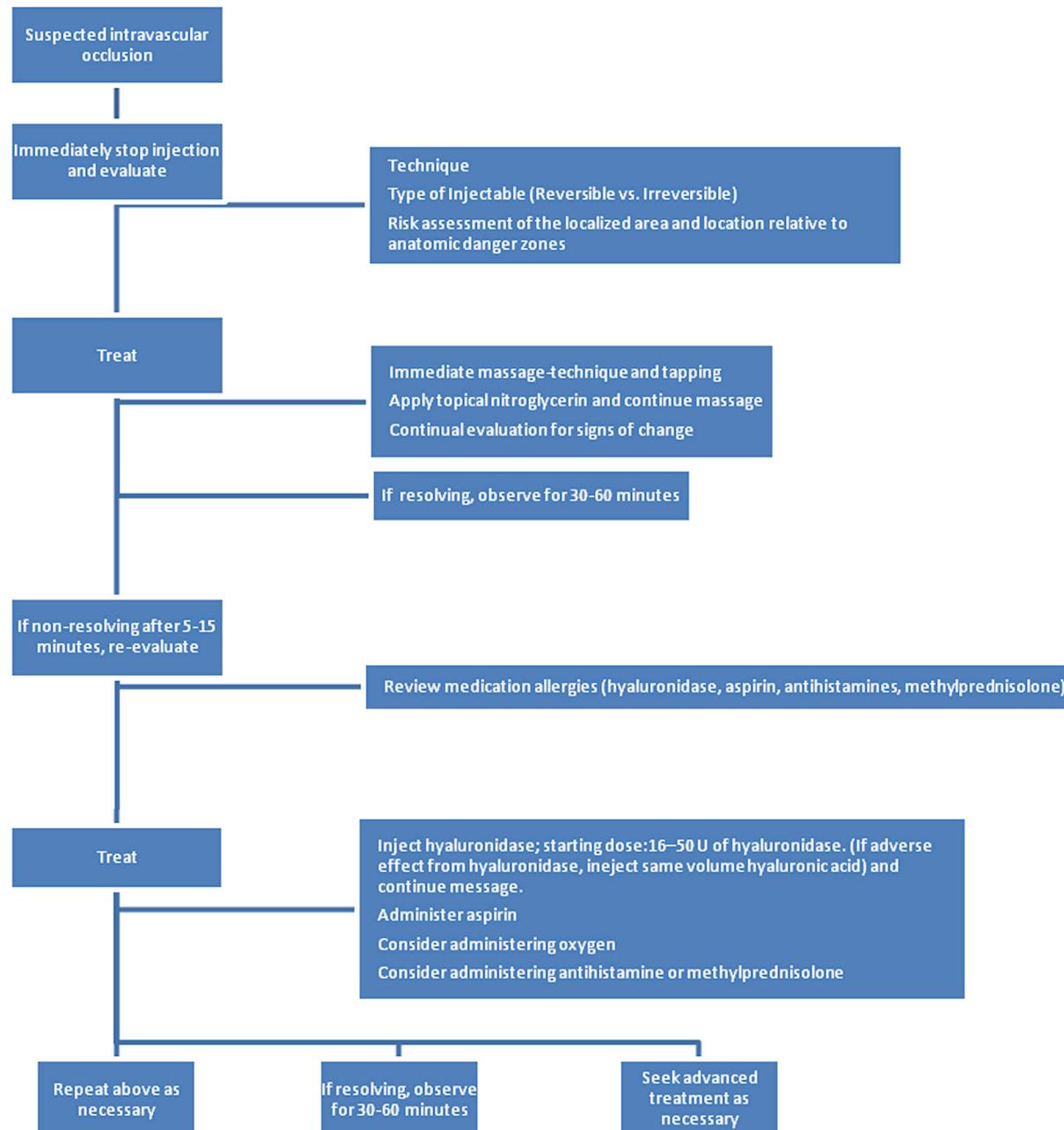


Fig 6. Outline of a treatment scheme for intravascular occlusion. Data from Nouri,¹⁷ Ozturk et al,⁶⁶ Kleyzman et al,⁶⁸ and Glaich et al.⁷³

appropriately to patient queries. Rather than simply reassuring patients complaining of pain and redness 1 to 2 days after filler injections, nurses and receptionists can be helpful in identifying these concerns as possible complications and expediting an office visit.

For sclerotherapy, similar use of careful technique can help to minimize complications. Pretreatment

evaluation is important to help identify patient-specific anatomic variations. Visual inspection, palpation, and duplex ultrasonography can aid in this initial evaluation. In addition, the choice of sclerosing solution, concentration, and quantity used should be selected not only to obtain optimal effect but also to minimize inflammation and potential complications.¹⁷

Treatment

Various algorithms have been offered to manage injectable filler-related vascular compromise, but none are supported by more than anecdotal evidence. If vascular occlusion is recognized during the treatment session, the injection is stopped, and an attempt is made to aspirate or extract the product. Measures may then be implemented to improve blood flow and dissipate the agent (Fig 6). Such steps may include aggressive massage, warm compresses, and the application of topical nitroglycerin paste to the affected area. Prompt vasodilation may reduce subsequent tissue vascular injury, although again this is more a theoretical supposition than an outcome validated by definitive evidence. If used, nitroglycerin paste may be applied every 4 hours assuming that the patient does not develop associated lightheadedness or headaches. Nitroglycerin is contraindicated in patients with methemoglobinemia and patients who are taking sildenafil, and should be used with caution in patients with hypotension, congestive heart failure, severe anemia, and some other cardiac or cerebral abnormalities. Oral sildenafil 50 mg daily may also be considered if nitroglycerin paste is not used.⁶⁴ When the filler in question is a derivative of hyaluronic acid, the perilesional injection of hyaluronidase is an important treatment strategy, because this may result in rapid dissolution of the injectant and concomitant release of the vasoocclusion. While full-strength hyaluronidase can be used, hyaluronidase is typically provided in concentrated solutions (eg, 200 units/cc), and it is therefore often diluted with lidocaine before injection to aid in pain control and then injected in several small volume boluses (eg, 0.1-0.5 cc each, with 40-80 units per cc dilution). Placement of a dilute solution at various points can enable diffusion of the enzyme throughout the affected area of tenderness and erythema, which may be poorly demarcated and quite broad in extent. Although some feel that intravascular injection cannot be undone by the use of hyaluronidase, the pressure effect of filler surrounding the affected vessel can be relieved by digestion of any adjacent filler that is surrounding the vessel. To diminish inflammation and facilitate tissue healing, potent topical corticosteroids and a short course of oral corticosteroids may be considered.⁶⁴

A course of aspirin or heparin products has also been advocated in these circumstances because of the antiinflammatory and antiplatelet effects and blood thinning properties, respectively. Some have promoted the use of topical oxygen emulsion, a cosmeceutical, to speed epithelialization, but while there are limited *in vivo* animal data suggesting this

therapy may accelerate wound healing, topical oxygen remains a speculative approach.^{66,75-77} Prompt recognition and swift intervention can potentially prevent progression to necrosis, but sometimes the tissue injury is too far along to be stopped. If skin necrosis ensues, local wound care with emollients may help. Oral antibacterial or antiviral products may be needed to prevent infection if significant tissue loss occurs. Early erythematous scars may be treated with vascular lasers and lights, such as pulsed dye laser and nonablative fractional resurfacing devices. Close patient follow-up is routine.

Fortunately, in most cases, vascular occlusion resolves with minimal or no sequelae. Extensive areas of reticulated erythema may remit entirely, and apparently severe events may leave only modest dyspigmentation and textural change. Glabellar and perinasal occlusive events appear most likely to result in significant scarring, but even so, this is relatively uncommon. Reassuring the patient and advising him or her to eschew aggressive corrective measures may be the best approach during the several weeks after the inciting event. Well-intentioned laser treatments and chemical peels in the immediate aftermath may aggravate the inflammatory process and possibly worsen the final outcome.

With respect to retinal artery occlusion, if symptoms of visual impairment occur, interventions aim to reduce intraocular pressure and dislodge the embolus to improve perfusion of the retina and optic nerve. There is no single reliable treatment for iatrogenic retinal artery embolism. For dermatologists, the primary recommended measure in this circumstance is immediate ophthalmologic consultation. Ophthalmology may choose to administer ocular massage, timolol eye drops, diuretics, hemodilution (with hydroxyethyl starch), corticosteroids, calcium channel blockers, anticoagulation, and needle decompression of the anterior chamber.⁶⁶ Quick action is crucial; while the injury may not be correctable despite timely interventions, all efforts should be made to have the patient be seen by an ophthalmologist within an hour of detection of the problem.

VENOUS THROMBOEMBOLISM: DEEP VEIN THROMBOSIS AND PULMONARY EMBOLISM

Key points

- Venous thromboembolisms have been reported to occur postsurgery (eg, Mohs micrographic surgery) and postprocedurally (eg, sclerotherapy)

- **Most cases of venous thromboembolism after dermatologic surgery have occurred in the setting of discontinued anticoagulation in individuals with underlying hypercoagulable states**
- **Clinical presentation of a deep vein thrombosis includes lower limb pain or swelling**
- **Presentation of pulmonary embolism includes pleuritic chest pain, tachypnea, tachycardia, dyspnea, cough, hemoptysis, and circulatory collapse**
- **Treatment options for deep vein thromboses or pulmonary embolisms include anticoagulation, an inferior vena cava filter or thrombolysis when indicated, and compression stockings**

General/incidence

Venous thromboembolism (VTE) encompasses both pulmonary embolism (PE) and deep vein thrombosis (DVT).⁷⁸ Overall, VTE affects approximately 100 per 100,000 persons per year in the United States. Given the prevalence of VTEs in the general population, and the increased incidence in hospitalized and immobilized patients, most dermatologists have at some point during training or in practice encountered spontaneously arising VTEs. Within the context of dermatologic surgery, VTEs have been reported to occur postsurgery (eg, MMS) and postprocedurally (eg, most reports have been associated with foam sclerotherapy). While DVT is a common adverse outcome after large surgical procedures on the lower extremities, such as orthopedic surgery, it is a much rarer occurrence after MMS, especially when patients have not immobilized the extremity.⁷⁹ Few reports of postoperative thrombotic or thromboembolic disease have been described in the dermatologic literature. The majority of reported cases have occurred in the setting of discontinued anticoagulation in individuals with underlying hypercoagulable states.⁷⁹ In particular, 2 cases of thromboembolic strokes soon after MMS occurred in patients who had discontinued their anticoagulants 1 week preoperatively and restarted warfarin 1 day after surgery. The superimposition of a rebound hypercoagulable on underlying predisposing conditions was likely associated with the adverse outcomes.^{79,80}

Other rare reported cases of VTE after MMS, including postoperative PE and a clotted prosthetic aortic valve, similarly occurred in the context of discontinuation of anticoagulation preoperatively in patients with hypercoagulable states.^{79,81} The exceptionally favorable safety profile of MMS, even

Table III. Postoperative risk factors for venous thromboembolism*

Albumin <3.5 mg/dL
Bilirubin >1.0 mg/dL
Chemotherapy ≤30 days
Contaminated wound
Disseminated cancer
Emergency surgery
Erythrocyte transfusion, >4U in the 72 hrs before surgery
Hematocrit <38%
High American Society of Anesthesiologist Class
Female sex
Infection
Operative dyspnea
Sodium >145 mmol/L
Type of surgical procedure
Ventilator dependence

*Data from Goodacre.⁷⁸

when performed on patients with therapeutic levels of anticoagulation,⁸² combined with reports of adverse outcomes upon discontinuation of anticoagulation, has led to the recommendation that anticoagulation be continued uninterrupted in most cases of dermatologic surgery.⁸¹

VTE has more commonly been associated with sclerotherapy. An estimated incidence of thromboembolic events after foam sclerotherapy of 0.003% can be calculated from a systematic review, which counts 40 events among 14,546 cases.³ Other publications cite rates of DVT and PE of 1% to 3%, and that of stroke as substantially lower (0.01%).⁸³ Similar to foam sclerotherapy, liquid sclerotherapy has also been associated with a small risk of VTE.⁶⁰ Factors influencing the occurrence of VTE include underlying patient characteristics (eg, a history of previous DVTs), aberrant venous anatomy, size of injected vessels, and the volume and concentration of the liquid sclerosant. More studies are needed to more precisely estimate the contributions of these factors.

Risk factors

Classically, risk factors for VTEs are conditions in which hypercoagulability, endothelial damage, and hemodynamic changes occur.²³ As such, VTEs often emerge after procedures and surgeries.⁷⁸ Other contributing causes include trauma, malignant conditions, oral contraceptive therapy, previous VTE or hereditary thrombophilia, increasing age, and immobility.⁷⁸ Blood pooling and stasis caused by a multitude of various factors, among which is venous compression, may contribute to thrombosis. Varicose veins and smoking may also play a role in the development of venous clots that can result in

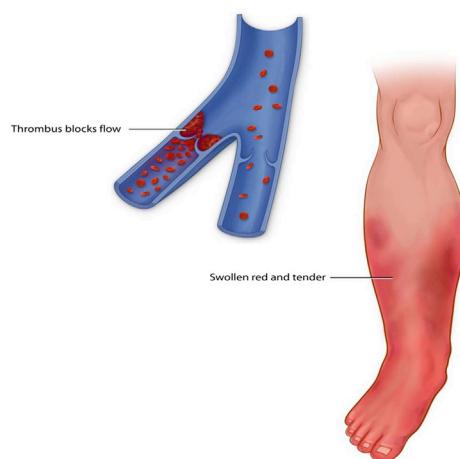


Fig 7. Pathophysiology of thrombus formation in a patient with deep vein thrombosis correlates to the clinically significant symptoms of a swollen, erythematous, and tender leg.

DVTs.⁷⁹ Table III lists postoperative risk factors for VTE. It has been shown that hospitalization is independently associated with an 8-fold increase in the relative risk for VTE.⁸⁴ However, because the overwhelming majority of dermatologic surgery is performed on ambulatory outpatients during a same-day procedure, the additional risk associated with hospitalization is eliminated.

Sclerotherapy has been described as a controlled thrombophlebitic reaction culminating in thrombosis and inflammation. As such, an undesirable, rare byproduct of sclerotherapy is a VTE.¹⁷ Two specific risk factors that relate to DVT during sclerotherapy include the experience of the treating physician and the amount of foam applied. The rate of postinterventional DVT is 5 times as high for patients of physicians with no or limited experience in sclerotherapy, compared to those with more experienced physicians.¹ According to Stucker et al,¹ physicians who are less experienced have a tendency to inject significantly more sclerosing foam. This, in turn, may account for the greater risk of adverse outcomes as amounts of foam >20 mL appear to increase the risk for DVT.

Clinical features

The clinical presentation of a DVT includes lower limb pain or swelling (Fig 7).⁷⁸ Warmth, erythema, and the Homan sign have limited diagnostic value.⁷⁸ Patients with concurrent pulmonary symptoms should be suspected of having a PE. A low-grade fever may also be present, especially with pulmonary infarction.⁸⁵ The presentation of PE includes pleuritic chest pain, tachypnea, tachycardia, dyspnea, cough, hemoptysis, and circulatory

collapse (eg, a low SBP or loss of consciousness).⁸⁶ A history of a previous DVT or VTE is a risk factor for subsequent VTEs, and therefore the index of suspicion should be raised for patients with a history of DVT or VTE who present with relevant symptoms.⁷⁸

Diagnosis/imaging tests

Once a VTE is suspected by a dermatologist, appropriate referral to the emergency department or to vascular surgery is made for additional assessment and management. While dermatologists are typically not involved in such additional management, for interest we consider the subsequent work-up.

The diagnostic work-up of a VTE is largely based upon a clinical prediction rule. A common one used for VTE (both DVT and PE) is the Wells score (Table IV). The Wells score relies upon the history and presentation of the patient to predict the likelihood of having a VTE and thereby to select appropriate diagnostics.⁸⁸ For the diagnosis of a PE, diagnostic strategies incorporate either a ventilation-perfusion scan or a helical CT scan.⁸⁷ Other ancillary tests that can aid in diagnosis include the D-dimer test. For the diagnosis of a DVT, testing is based on pretest probability of DVT. For patients with a lower probability of a DVT, a D-dimer level may be used as a measure to effectively rule out DVT.⁷⁸ If D-dimer testing is unavailable or unreliable—because of falsely elevated levels such as those seen postprocedure or postsurgery—ultrasonography may be used (with a sensitivity of 63-94% based on anatomic location).^{78,89} For patients with a high probability of DVT or a positive D-dimer result, venous ultrasonography is used to diagnose or exclude DVTs.⁷⁸ Negative ultrasonographic results effectively rule out proximal DVT but not distal DVT. About 1% to 2% of patients with normal initial ultrasonographic results have calf venous thrombosis that is destined to extend into the proximal veins, generally within 5 to 8 days. For this reason, ultrasonography is often repeated 1 week later if initial investigation is negative.⁷⁸ Ultrasonography is considered the criterion standard and most cost effective noninvasive imaging procedure for the diagnosis of DVT. According to the American College of Radiology Expert Panel on Vascular Imaging, there is little evidence to support the use of CT venography lower extremity and pelvis with contrast (CTV) to diagnose DVT other than as a work-up for PE. However, CTV may be considered for pelvic DVT when a patient is unable to undergo ultrasonography (eg, when a patient is in a cast), or when ultrasonography is nondiagnostic. In addition,

Table IV. Computing the Wells score from the clinical findings

Clinical findings
Paralysis, paresis, or recent orthopedic casting of lower extremity (1 point)
Active cancer (chemotherapy ≤180 days or palliative or disseminated cancer) (1 point)
Recent immobility (>3 days) or major surgery within past 4 weeks (1 point)
Localized tenderness within deep venous system (1 point)
Edema of entire leg (1 point)
Calf edema (by >3 cm when compared with the asymptomatic leg [measured 10 cm below tibial tuberosity]) (1 point)
Pitting edema greater in symptomatic leg (1 point)
Collateral superficial veins (nonvaricose) (1 point)
Alternative diagnosis as likely or greater than that of deep vein thrombosis (-2 points)

Deep vein thrombosis (DVT) risk scores interpretation: 3-8 points: high probability of DVT; 1-2 points: moderate probability of DVT; -2 to 0 points: low probability of DVT.

Adapted with permission from Wells PS, Anderson DR, Bormanis J, et al. Value of assessment of pretest probability of deep-vein thrombosis in clinical management. *Lancet* 1997;350:1795-8.

magnetic resonance venography lower extremity and pelvis without and with contrast may be considered in such instances. Magnetic resonance venography lower extremity and pelvis without and with contrast and CTV are superior to ultrasonography for indicating the overall venous clot burden, evaluating extravascular anatomy, and evaluating alternative diagnoses.⁹⁰

Prevention

A personal history of DVT is a relative contraindication to foam sclerotherapy. If foam sclerotherapy is to be pursued in such patients, however, certain modifications and precautions are recommended. Patients with a history of DVT or PE typically receive Doppler ultrasonography of their legs before sclerotherapy. In addition, some clinicians recommend effective anticoagulation prophylaxis with low molecular weight heparin (LMWH; enoxaparin 40 mg once per day for 3 days postsclerotherapy) and physical DVT prophylaxis with compression therapy (23-32 mm Hg).⁹¹ Lower concentrations of sclerosant and lower volumes of foam should be used whenever possible.¹ In the absence of a clear contraindication, such as severe peripheral arterial disease, fragile skin, or severe edema, graduated compression stockings or intermittent pneumatic compression may serve as primary prophylaxis against postoperative DVT. Mechanical compression can be used as monotherapy in patients for whom the risks of anticoagulation outweigh the benefits.⁷⁸

Perioperative withholding of antithrombotics in cutaneous surgery may be associated with serious adverse vascular events.^{79-81,92} In addition, although continuing antithrombotics may increase bleeding complications, the overwhelming majority of these do not lead to serious adverse outcomes.^{93,94} While

in general it is not recommended to discontinue anticoagulation before dermatologic surgery, the final decision should be made by the surgeon after evaluation of patient history, assessment of tumor location and characteristics, and consideration of other patient-specific risks of continuing anticoagulation. If appropriate, consultation with other experts is recommended.⁸¹

Although the favorable safety profile of cutaneous surgery precludes obtaining routine preoperative clearance or preoperative laboratory tests, such as coagulation studies, a thorough preoperative history is important for determining if such laboratory assessments may be warranted (ie, a recent history of an unstable international normalized ratio, recent bleeding episodes, a history of problems with coagulation after procedures, etc). Therefore, the decision to evaluate the international normalized ratio in patients who are taking warfarin should be made on a case by case basis as deemed appropriate by the dermatologic surgeon. Recently, several newer anticoagulants have received approval by the US Food and Drug Administration. These include dabigatran, rivaroxaban, and apixaban. Unlike warfarin, clinical monitoring is not required, with laboratory testing to verify levels consequently not performed. As with other anticoagulants, routine discontinuation of these newer anticoagulants is not recommended before cutaneous surgery because the risk of adverse events caused by discontinuation is believed to usually exceed in magnitude and frequency the risk of adverse events from performing cutaneous surgery with active pharmacologic anticoagulation. If, however, the dermatologic surgeon does determine that discontinuation is necessary, consultation with the prescribing physician may be obtained to ensure this is feasible and to enlist the guidance of the

prescribing physician regarding the mode of implementation. When discontinuation is deemed appropriate, and in patients with normal kidney function, dabigatran is typically stopped ≥ 48 hours before the procedure, and rivaroxaban and apixaban 24 hours before. In patients with impaired creatinine clearance, dabigatran may be discontinued 3 to 4 days before surgery, and rivaroxaban and apixaban 48 hours before.⁹⁵⁻⁹⁷

Management

Most patients with confirmed DVT can be safely treated as outpatients with LMWH unless they have suspected PE. Patients with suspected PE usually receive hospital treatment by appropriate medical or surgical services.⁷⁸ Treatment options for DVTs or PE include anticoagulation, and inferior vena cava filter or thrombolysis when indicated, and compression stockings ≤ 1 month of diagnosis of proximal DVT and continued for a minimum of 1 year.⁷⁸ Referral to the patient's primary care physician or a specialist for appropriate management of thromboembolic events is also recommended.

LMWH is often the initial treatment for DVT, but unfractionated heparin may be used in patients with severe renal impairment or to achieve rapid anticoagulation in massive DVT.^{12,78} If warfarin is to be used, it is started at the same time as heparin. Heparin is continued concomitantly with warfarin until the therapeutic potential of warfarin is achieved. Although it is more expensive, long-term treatment with LMWH is a safe and effective alternative for patients in whom oral anticoagulation is not appropriate because of difficulty in titrating dose, poor patient adherence to monitoring, or adverse effects.⁷⁸ Of note, warfarin has many interactions with other drugs and foods that can decrease warfarin absorption (eg, cholestyramine and colestipol), enhance warfarin clearance (eg, phenytoin, rifampin, and glutethimide), potentiate warfarin action (eg, acetaminophen), and inhibit warfarin metabolism (eg, omeprazole and miconazole).⁷⁸ Notably, brief courses of perioperative drugs, such as analgesics and antibiotics, can generally be safely administered to patients who are taking anticoagulants, including warfarin. The duration of anticoagulation therapy should be primarily determined by the details of the inciting events and underlying issues.⁷⁸ Complications of anticoagulation include bleeding, heparin-induced thrombocytopenia, anticoagulant skin necrosis, postthrombotic syndrome, hypersensitivity reactions, osteoporosis, and elevation of liver enzymes.⁷⁸

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Dermatologic surgery emergencies



Complications caused by systemic reactions, high-energy systems, and trauma

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Learning objectives

After completing this learning activity, participants should be able to describe management options of each specific type of emergency that can result from dermatologic surgery, lasers, and cosmetic surgery.

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While the overall incidence of emergencies in dermatologic surgery is low, emergent situations can occasionally pose a risk to patients undergoing such procedures. The clinical importance of several types of emergencies related to systemic reactions, high energy systems, and trauma are reviewed, and relevant epidemiology, clinical manifestations, diagnosis, work-up, management, and prevention are discussed. Early detection of surgical emergencies can mitigate any associated adverse outcomes, thereby allowing the outstanding record of safety of dermatologic surgery to continue. (*J Am Acad Dermatol* 2016;75:265-84.)

Key words: anaphylaxis; arrhythmia; complication; dermatologic emergency; fire; hematoma; laser injury; lidocaine toxicity; trauma.

Despite the high level of safety and low adverse event rates associated with office-based dermatologic surgery, emergencies can arise, and it is helpful for dermatologists to be able to identify the onset of these. Prompt recognition and appropriate management can minimize detrimental patient outcomes and ensure that dermatologic surgery maintains its privileged position as an unusually safe surgical specialty.

Many of the adverse events and emergencies considered in this review are uncommon or rare.

Abbreviations used:

ACLS:	advanced cardiovascular life support
BLS:	basic life support
CPR:	cardiopulmonary resuscitation
EMI:	electromagnetic interference
EMS:	emergency medical services
RBH:	retrobulbar hematoma or hemorrhage

Nonetheless, we include these for completeness. In addition, many of these uncommon problems are by

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nature unpredictable and idiosyncratic, often associated with few if any steps that a dermatologist can reasonably preemptively implement to avoid their occurrence. Finally, while we generally include a detailed methodology for addressing and managing each adverse event, the portion of such management that is performed by the dermatologist is limited. In many and likely most situations, the dermatologist's role is merely to identify that something is wrong, and then to make a referral to another specialist. A simplified description of what may be done by nondermatologists is included to help the dermatologist refer to the correct service and communicate with the doctor receiving the referral, and not because the dermatologist is responsible for further management.

The first part of this review addressed complications that may occur during dermatologic surgery caused by occlusion and blood pressure. This second article in the series will consider problems that are more likely to occur because of systemic reactions, high-energy systems, or trauma.

ANAPHYLAXIS

Key points

- **Anaphylaxis is the most dramatic and potentially catastrophic manifestation of immediate hypersensitivity**
- **Severity of reactions can vary widely from mild pruritus and urticaria to shock and death**
- **The key to anaphylaxis management is prompt recognition**
- **Intramuscular epinephrine is the first-line treatment of patients with suspected anaphylaxis**

General/incidence

Anaphylaxis is a potentially catastrophic manifestation of immediate hypersensitivity with the release of numerous proinflammatory, vasoactive substances leading to vasodilation with increased vascular permeability, edema, bronchospasm, and bronchoconstriction.

Data regarding the incidence and prevalence of anaphylaxis are limited, with no available incidence data for dermatologic surgery. Apart from previous exposure, no known epidemiologic characteristics exist that can reliably identify those at risk for anaphylactic sensitivity. In the hospital setting, medications (especially penicillins and anesthetic agents during the perioperative period) and radiographic contrast agents are the most common causes of anaphylaxis.^{1,2} Medications are a relatively more common cause of anaphylaxis in adults compared to

children (~10% vs ~1%), unlike foodstuffs, which are more associated with childhood anaphylaxis (~5% vs ~30%). The majority of both adult and child anaphylaxis cases are caused by insect venom (80% vs 60%).³ In many cases of anaphylaxis, no cause can be determined. Overall, the lifetime risk of anaphylaxis in the United States is estimated to be $\geq 1.6\%$, with anaphylaxis accounting for >100 deaths annually.⁴

Although the specific incidence of anaphylaxis in dermatologic surgery is not known, it is conceivable that anaphylaxis can occur because of preoperative administration of a penicillin or cephalosporin for endocarditis or wound prophylaxis, local injection of an ester anesthetic or lidocaine with methylparaben, or less likely events, such as bee stings or ingestion of particular foods.^{5,6} Muscle relaxants and latex are the most common causes of anaphylaxis during surgical procedures. Of particular concern during dermatologic surgery is latex because of the prevalent use of products containing latex (eg, gloves and instruments), which may be the causative basis for the increasing incidence of latex anaphylaxis.⁷ Anaphylaxis has been described in several cases as being caused by the topical application of antibiotics, such as bacitracin, or chlorhexidine.⁸⁻¹¹ Reported cases typically involved patients with stasis dermatitis or ulceration, which may have rendered them susceptible to rapid systemic absorption of the topical agent. Administrations of pain-reducing medications (eg, nonsteroidal antiinflammatory drugs and narcotics, such as morphine and meperidine) have also been associated with anaphylaxis.^{7,12} Another rare cause of anaphylaxis in dermatologic surgery is the intravascular chemical agent used in sclerotherapy. Anaphylaxis to such agents can occur in sclerosant-naïve patients, or in patients with a previous exposure or history of tolerance to subsequent retreatment. As such, patients with anaphylactic reactions should be carefully monitored to ensure that an episode that has apparently subsided does not recur, in the short-term or the more distant future.^{13,14}

Clinical features

The severity of reactions can vary widely from mild pruritus and urticaria to shock and death. Prodromal features include diffuse erythema, pruritus, or urticaria; these may be followed by inspiratory stridor, laryngospasm, bronchospasm, hypotension, cardiac arrhythmia, and hyperperistalsis, or any combination thereof (Fig 1). The progression of symptoms can occur as outlined in Table I. Rapid onset culminates in a rapid peak of severity within 5 to 30 minutes, and potential consequences include shock and death.¹⁵

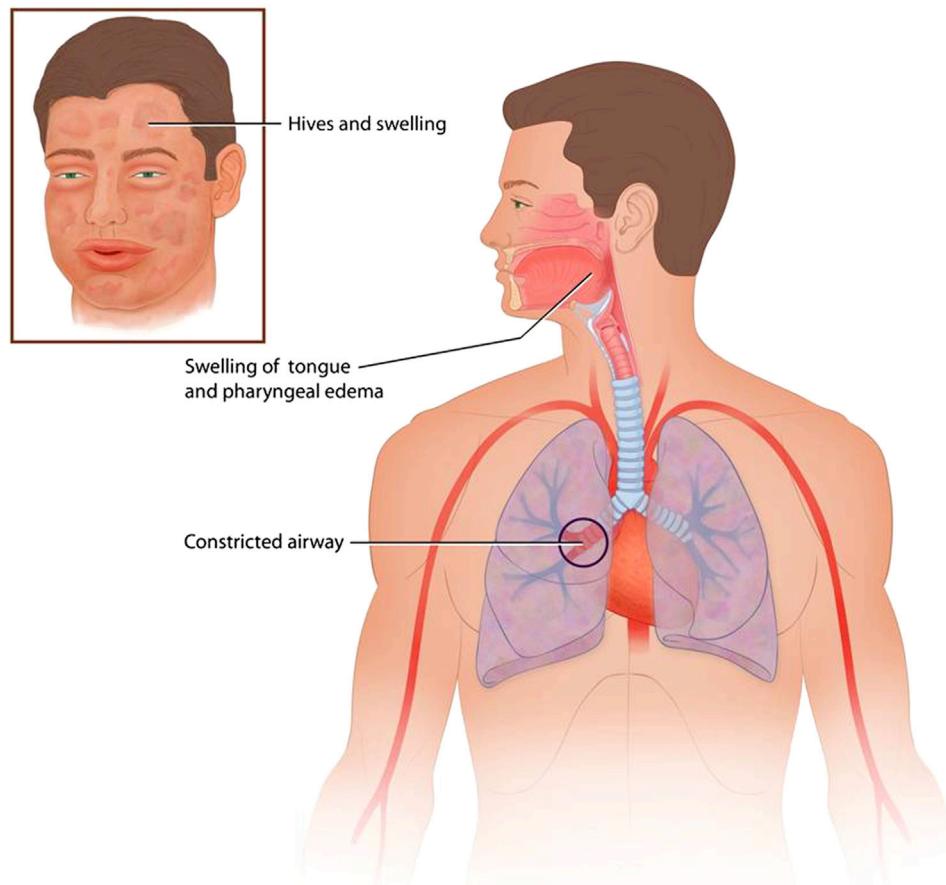


Fig 1. Common clinical features of anaphylaxis.

Table I. Progression of anaphylaxis

Stage	Symptoms and signs
I	Itching, flush, urticaria, and angioedema
II	Itching, flush, urticaria, angioedema (not obligatory), nausea, cramps, rhinorrhea, hoarseness, dyspnea, arrhythmia, tachycardia (increase $\geq 20/\text{min}$), and hypotension (decrease $\geq 20 \text{ mm Hg}$ systolic)
III	Itching, flush, urticaria, angioedema (not obligatory), vomiting, defecation, bronchospasm, cyanosis, and shock
IV	Itching, flush, urticaria, angioedema (not obligatory), vomiting, defecation, respiratory arrest, and circulatory arrest

Diagnosis

The diagnosis of anaphylaxis is predicated on the prompt recognition of symptoms as described in Table I. Concurrent with the implementation of primary management measures, like administration of intramuscular epinephrine (eg, EpiPen), the dermatologist should ensure that emergency medical services (EMS) are activated. Immediate referral to an emergency physician is indicated.

Management

The key to anaphylaxis management is prompt recognition, upon which referral to EMS should be made. Identification of the inciting agent can help

ensure appropriate avoidance. In addition, an essential part of management is immediate treatment with appropriate pharmacologic or immunologic therapies. The patient should be placed in a supine position on the examining table, preferably in the Trendelenburg position, with loosening of tight clothing. Oxygen should be administered by face mask at low flow (1-2 L/min) and vital signs assessed. An effort should be made to eliminate exposure to the causative antigen if this is identified. Such efforts include wiping off any topical medication or applying a tourniquet proximal to the site of antigen injection and loosening the tourniquet every 5 minutes.¹⁶ As soon as EMS arrives, the patient's care

should be transferred. Intramuscular epinephrine in the midanteriorlateral thigh is the first-line treatment of patients with suspected anaphylaxis.¹⁷ Epinephrine is an alfa-1-agonist (which causes increased peripheral vascular resistance and decreases urticaria), a beta-1-agonist (causing increased cardiac rate and contractility), and a beta-2-agonist (which leads to relaxation of bronchial smooth muscles). Timely administration is essential; epinephrine should be administered intramuscularly as soon as anaphylaxis is suspected.¹⁸ The dose is 0.01 mg/kg of a 1:1000 (1 mg/mL) solution to a maximum of 0.5 mg in adults or 0.3 mg in children. Depending on the severity of the episode and the response to the initial injection, this dose can be repeated every 5 to 15 minutes as needed to counteract the rapid inactivation of the injectant; however, most patients respond to 1 or 2 doses.⁷

The need for additional medications after transfer to EMS depends on the severity of the reaction and the initial response to epinephrine. Oral antihistamines are second-line supportive therapy with a slow (>1 hour) onset of action and may be useful for control of urticaria and angioedema.⁷ An inhaled beta-agonist can be used as adjunctive therapy for patients with preexisting asthma who present with respiratory symptoms.¹⁸

While waiting for EMS, basic life support including cardiopulmonary resuscitation (CPR) may be initiated if safe and appropriate, and an open airway maintained through head tilt or jaw thrust maneuvers. Upon arrival of EMS, advanced cardiovascular life support (ACLS) may be initiated if necessary. Typically, regardless of clinical status, the patient may be hospitalized for a recommended 24-hour observation period given the potential for a relapse.

CARDIAC ARRHYTHMIA

Key points

- Cardiac arrhythmias are associated with multiple etiologies, some of which can occur during dermatologic interventions
- Instances of cardiac arrhythmias during phenol chemical peels have been described
- Ventricular arrhythmias, especially ventricular fibrillation, herald a life-threatening emergency and must be managed promptly
- Clinical features of ventricular fibrillation include faintness, loss of consciousness, seizures, and apnea
- Successful management of cardiac arrest is based on adequate cardiopulmonary resuscitation and, in the context of ventricular

fibrillation/ventricular tachycardia, attempted defibrillation within minutes of collapse

- Electrosurgery should be performed with caution, and away from the immediate proximity of the implanted device, in patients with cardiac pacemakers and defibrillators

General/incidence

Cardiac arrhythmias are abnormalities in heart rate or rhythm.¹⁹ The true incidence of arrhythmia in dermatologic surgery is unknown.¹⁹ While some arrhythmias may be benign in nature, others herald life-threatening emergencies and impending cardiac arrest.¹⁹

Risk factors

In dermatologic settings, cardiac arrhythmias have a range of possible etiologies, and may be idiopathic, of genetic origin (ie, tuberous sclerosis), medication-related (eg, phenol, epinephrine, and rituximab), and associated with disease states (eg, sarcoidosis, systemic lupus erythematosus, and systemic sclerosis).²⁰⁻²⁶ Particularly relevant to dermatologic surgery is phenol, an agent sometimes used in deep chemical peels, which has been related to cardiotoxicity.^{22,23} While phenol has been shown to cause cardiac arrhythmias in animal models,²² the data are less unequivocal in humans.²⁷ In a study by Price et al,²⁷ the authors found arrhythmias in patients undergoing phenol chemical peels, but most arrhythmias were attributed to anxiety because they were observable preoperatively rather than intra- or postoperatively. However, in a study by Truppman and Ellenby, a small number of patients undergoing phenol peels showed evidence of cardiac arrhythmias (including ventricular tachycardia in 2 patients). Data from this article suggest that the duration of the chemical peel correlates to the development of cardiac arrhythmia.²⁸ Gross et al²⁹ monitored serum levels of phenol and assessed cardiac arrhythmias in patients and observed no relationship between phenol level and cardiac arrhythmias. In addition, medications used for local anesthesia (eg, lidocaine and epinephrine) have the potential to lead to cardiac arrhythmia.³⁰⁻³² However, it is uncommon, because the amount of local anesthesia required for this would drastically exceed maximum recommended dosages. While these authors recognize that electrocardiographic findings (eg, a prolonged PR interval, supraventricular tachycardia, and widening of the QRS complex) can occur because of a local injection of anesthesia, the presence of rapid onset symptoms (further described below) or cardiac arrest more likely suggests intravascular injection if the dose falls

within recommended values. We discuss the emergency of ventricular fibrillation and its most severe complication, cardiac arrest.

Clinical features

The presentation of new onset atrial fibrillation may be difficult to identify because approximately 25% of patients may be asymptomatic. In addition, nonspecific symptoms are classically associated with this condition, such as fatigue, dyspnea, effort intolerance, palpitations, and lightheadedness.³³ Clinical features of ventricular fibrillation include faintness, loss of consciousness, seizures, and apnea. Typically, blood pressure is unobtainable and heart sounds are absent. If prolonged, ventricular fibrillation will result in death from cardiac arrest.²⁰

Diagnosis

Conscious victims, especially those with a heart rate >150 beats per minutes or symptoms of hypotension, altered mental status, ischemic chest discomfort, hypotension, or symptoms of acute heart failure should be transferred to the nearest EMS system because of the difficulty in distinguishing tachyarrhythmia (eg, sinus tachycardia and atrial fibrillation) without an electrocardiogram.³⁴ While it may be prudent to preemptively identify a high heart rate from easily reversible causes (eg, anxiety), this is not always a simple determination, and clinical judgment should err on the side of patient safety.

Appropriate activities at initial contact with the unconscious victim include diagnostic maneuvers and basic cardiopulmonary support interventions.³⁵ Circulation, airway, and breathing is assessed by testing for a response to voice, observing respiratory movements, noting skin color, and simultaneously palpating major arteries for a pulse.³⁵ The absence of a carotid or femoral pulse, particularly if it is confirmed by the absence of an audible heartbeat, is a primary diagnostic criterion.³⁵ The absence of respiratory efforts or the presence of agonal breathing, in conjunction with an absent pulse, is diagnostic of cardiac arrest.³⁵ Once a life-threatening incident has been suspected or confirmed, it is essential to contact EMS (9-1-1).

Survival from ventricular fibrillation or cardiac arrest may require both basic life support and ACLS, with integrated post–cardiac arrest care.^{20,34} In most outpatient dermatology offices, the infrastructure is not in place to administer more advanced life support, such as cardiac medication and line placement. Detailed information regarding appropriate techniques is provided by local basic life support classes, ACLS classes, and American Heart Association guidelines.³⁴

Management

Management of cardiac arrhythmias requires prompt transfer of care to an emergency physician or cardiologist. Successful management of cardiac arrest is based on high-quality CPR, and, for ventricular fibrillation/ventricular tachycardia, attempted defibrillation within minutes of collapse.³⁴ In addition to high-quality CPR, the only rhythm-specific therapy proven to increase survival to hospital discharge is defibrillation of ventricular fibrillation/ventricular tachycardia.³⁴

Pacemakers or implantable cardioverter defibrillators are common in the elderly population, who are also at risk for skin cancers and may need dermatologic surgery.³⁶ Although historically there has not been a consensus, some literature suggests that electrosurgery may affect implantable cardiac devices.^{28,36,37} Electrosurgery is an integral part of dermatologic procedures and cannot easily be routinely avoided, and therefore it has been deemed important to identify patients with implanted devices who are at greatest risk.^{36,37} Over time, technologic improvements have made pacemakers more resistant to electromagnetic interference (EMI), but this risk has not been eliminated.³⁶ Electrosurgery can result in pacemaker malfunction by oversensing, inhibiting of firing or triggering of rapid firing, device reprogramming, battery depletion, or direct damage to the device.^{36,37} Among these, inhibition is the most common and occurs when EMI is misinterpreted as physiologic cardiac activity, resulting in the pacemaker not sensing and failing to fire. This can result in temporary bradycardia or asystole if the patient is pacemaker-dependent, and may lead to inadequate cardiac output if pacemaker function is not restored.^{36,37} A study by LeVasseur et al²⁸ found evidence in the nondermatologic literature that electrosurgery may interfere with implantable cardioverter-defibrillators and pacemakers.²⁸ Matzke et al,³⁶ who monitored a group of 173 patients with pacemakers and 13 with implantable cardioverter-defibrillators undergoing dermatologic surgery, detected no complications from electrosurgery. In this study, certain pre- and perioperative precautions were undertaken to prevent a malfunction from occurring. More recently, Weyer et al³⁸ developed an ex vivo model to test risk of electrosurgery in dermatologic surgery by using a collagen-based saline gel in combination with 3 implantable pulse generators (pacemakers) and 3 implantable cardioverter defibrillators (Fig 2). When hyfrecators were tested on the apparatus under normal settings (10 W) and maximum power (30 W), measured EMI showed no interference with the defibrillators and pacemakers, except when the hyfrecation was



Fig 2. Simulation device for assessing disruption of implanted cardiac device by proximal cautery. Reproduced with permission.³⁵

immediately adjacent to the cardiac devices. For pacemakers, atrial inhibition occurred at a distance of 3 cm at maximum hyfrecator power and 1 cm at normal power; ventricular inhibition was only seen at a distance of ≤ 1 cm.³⁸

Table II lists some important precautions that can help to avoid adverse events from cardiac implantable devices during dermatologic surgery. In addition, in certain very high-risk patients, it is advisable to coordinate care with the patient's cardiologist to minimize any risk and decide on an effective plan for safe surgery.

FIRE

Key points

- Each year in the United States there are approximately 50 to 650 surgical fires, the majority of which involve electrosurgical or laser devices
- Three elements are commonly required to initiate and maintain a fire: an ignition source, a fuel, and an oxidizer
- Specific steps can be taken pre- and perioperatively to help prevent surgical fires

General/incidence

Surgical fire is a rare but potentially life-threatening complication. Such fires occur as often as several hundred times in the United States each year and are usually caused by the use of electro-surgical or laser devices.³⁹⁻⁴¹ The true incidence may be higher because only an estimated 1 in 10 to 1 in 100 fires are well-documented because of a lack of centralized reporting.^{40,41} Monopolar electrosurgical units and laser devices are the most common causes.^{42,43} In the context of dermatologic surgery, Waldorf et al⁴⁴ reported a flash fire caused by a pulsed dye laser that resulted in a partial thickness burn. Another case report noted second- and third-degree burns after the inadvertent firing of a

Table II. Preventive measures to minimize risk to patients with implantable cardiac devices during cutaneous electrosurgery*

Consider use of heat electrocautery
Consider use of bipolar forceps
Use short bursts of electrical activity
Use low voltage and power
Avoid use of cautery or hyfrecation immediately adjacent to the pacemaker
If the cardiac device must be deactivated, minimize deactivation time and reactivate promptly
Pacemaker-dependent patients may be placed in an asynchronous (fixed rate) pacing mode

*Data from Darling²⁶ Weyer et al.³⁸

carbon dioxide laser that ignited a smoldering spot on a surgical towel.⁴³

Pathophysiology/risk factors

Three elements are commonly required to initiate and maintain a fire: an ignition source, a fuel, and an oxidizer.^{43,45} Electrosurgery units and lasers are both potential ignition sources. The inherent flammability associated with these devices in dermatologic surgery is poorly understood, because most available data pertain to surgical procedures conducted under general anesthesia.^{46,47} To better understand the risk of fires in dermatology, Arefiev et al⁴⁶ performed a series of experiments to assess the flammability of various materials and devices. Carbon dioxide lasers were found to create more smoke, char, and flame than electrofulguration and electrodessication.⁴⁶ In addition, a carbon dioxide laser on a dry underpad or cotton caused a flame to be produced.⁴⁶

There is an increased likelihood of ignition when electrosurgical laser devices are used in high-oxygen environments.⁴⁴ Some source of oxygen supplementation was a contributing factor in 74% of all surgical fires.⁴³ To prevent this risk, bipolar electrosurgery has been suggested for use in environments when oxygen supplementation is required.⁴⁸ In addition, it has been recommended that supplemental oxygen be stopped at least 1 minute before and during the use of the ignition source.⁴⁹ Supplemental oxygen is a common oxidizer in surgical fires, but ambient oxygen can also be sufficient as an oxidizer.⁴⁷

Numerous materials ubiquitous in the health care setting can serve as fuels. Gauze, drapes, towels, underpads, and cotton have all been experimentally shown to be potential fuel sources.⁴⁶ Other surgical supplies and instruments can also fuel fires.⁴³ One study investigating the flammability of surgical drapes with continuous firing of a carbon dioxide laser found that all tested drapes ignited in

Table III. Preventive measures to avoid fire during cutaneous procedures*

Time	Measures
Days before surgery	Instruction regarding fire safety to all health care personnel; checklists, time-outs, or procedures to identify and remove potential fuel sources; and have available and properly maintained fire extinguishers
Hours before surgery	Minimize the use of alcohol-containing products; remove extraneous fuel sources if in proximity to the treatment site; and allow prepping agents to dry completely before draping the patient
During surgery	Direct gases (eg, oxygen, nitrous oxide, etc) away from the laser field; keep unavoidable potential fuel sources moist throughout the procedure Minimize use of cautery and ignition sources near the airway Consider briefly turning off supplemental oxygen with pulse oximetry monitoring during laser or cautery use

*Data from Arefiev et al,⁴⁶ Pierce et al,⁴⁷ Batra and Gupta,⁵¹ Cao et al,⁵⁴ and Rohrich et al.⁵⁵

oxygen-enriched environments.⁵⁰ Conflicting data have emerged regarding the risk of fire in the vicinity of alcohol-based fuel sources. Case reports have documented fires that used alcohol-based skin preparations as fuel.⁵¹⁻⁵³ However, materials saturated with isopropyl alcohol were not easily ignited by Arefiev et al.⁴⁶ Aluminum chloride, chlorhexidine, and isopropyl alcohol may also fuel fires, and aluminum chloride and chlorhexidine may be particularly flammable in circumstances where these materials have not fully dried. As such, it is recommended that these preparations be allowed to dry completely before proceeding with use of the laser or surgery.^{46,49}

Prevention

In high-risk environments, checklists and time-outs can help identify potential fuel sources in the surgical field.⁴⁷ Specific preventive steps can be taken before and during the surgery (Table III). In addition, intraoperative supplemental oxygen should be delivered at the lowest concentration possible.⁴⁷ Less flammable equipment and materials (eg, phenol polymer drape, water-based prepping agents, and red rubber endotracheal tubes [when using a carbon dioxide laser]) may be substituted for more flammable equipment and materials (eg, a cotton/polyester drape, alcohol-based prepping agents, and polyvinylchloride endotracheal tubes).⁴⁷ Staff should also ensure that water and fire extinguishers are readily available.⁵⁴

Treatment

A fire management plan developed in conjunction with a safety officer should be rehearsed by all operative personnel. Surgical fires can spread rapidly; prompt action should be taken to extinguish the fire. Necessary steps may include patting out a small fire with a gloved hand or towel. Large fires may require a more comprehensive response, such

as stopping the flow of oxidizers, removing the burning materials, extinguishing them, and attending to the care of the patient.⁴³ If the fire cannot be extinguished by materials available nearby, other means may include fire extinguishers, fire blankets, sprinkler systems, or evacuation and handover to firefighters.⁴³ Local wound care is based on the degree of the burn, the percentage of body surface area involvement, and specific patient and wound characteristics.

LASER EYE INJURY

Key points

- Eye safety is of the utmost importance during laser therapy
- When an eye injury does occur, wavelength, exposure duration, and laser intensity are all primary factors in determining the extent of the injury
- Injury to the eye may be temporary, but it also has the potential to result in permanent vision loss
- Laser eye injury should motivate emergent ophthalmologic referral
- Management of laser-mediated retinal injury is designed to reduce the inflammatory response
- While eye protective measures like laser goggles and corneal shields provide efficacious protection from laser injury, the wavelength band rejection, optical density, and location of the shield on the face of the wearer determine the level of effectiveness

General/incidence

Multiple cases of lasers causing eye injuries have been reported. These have resulted from inappropriate laser use, insufficient eye protection (eg, placement of a hand over the eye for protection rather than appropriate goggles or eye shields), and

other accidents. The true incidence of eye injuries caused by lasers is unknown because of the lack of large cohort studies. Where and to what extent laser energy injures the eye is associated with the specific wavelength administered. Laser light in the visible to near infrared spectrum (ie, 400-1400 nm), also known as the “retinal hazard region,” can cause damage to the retina resulting in scotoma (a blind spot in the fovea). Laser light in the ultraviolet (ie, 200-400 nm) or far infrared (ie, 1400-10,600 nm) spectrum can damage the cornea or lens. Exposure to the Q-switched 1064 nm neodymium-doped yttrium aluminium garnet laser is particularly dangerous and may initially go undetected because of the invisibility of the main laser beam, the lack of a visible secondary aiming beam, and the absence of sensory nerves on the retina (Fig 3). Perhaps the largest number of anecdotal incidents of eye injury has followed epilation with laser hair removal around the eyelid. This is not surprising because laser hair removal is a common procedure, often practiced in a less-controlled nonphysician office setting, and is notable for targeting pigmented structures, which are prevalent in the ocular globe. Injury after laser hair removal treatments has resulted in cataract formation and iris atrophy, as observed after the use of a diode laser in the absence of protective eye shields.⁵⁹ Several cases of posterior synechiae, conjunctival hyperemia, photophobia, reduced visual acuity, and pigmentary cells in the chambers of the eye have also been reported after laser epilation of the eyebrow region without adequate eye protection.⁶⁰ Anterior uveitis has developed after similar treatments with the 755-nm alexandrite laser.

Although most laser eye injury cases derive from intraprocedure eye exposure, there are reports of eye injury despite shield placement. One such case was associated with laser hair removal to the eyebrow using the 800-nm diode laser.⁶¹ Shifting or slippage of eyewear may have been responsible, or laser light reflected by other structures, such as bone, may have entered the eye indirectly. Laser operators sometimes injure themselves when they are too engrossed in a treatment to realize that they are themselves inadequately protected, or when they handle the laser without realizing it is in ready mode. A traumatic macular hole developed in a physician assistant who was performing routine maintenance of a 755-nm Q-switched laser, did not realize the laser was on and ready, and had line of sight with the active beam.^{62,63} Vitreous floaters can easily be induced by various lasers, including the pulsed dye laser, which was implicated in vitreous floaters induced in a dermatologic

Electromagnetic Wavelength	Damage to the eye	Damage to the skin
UV-C (200-290 nm)	Photokeratitis	Erythema Skin cancer
UV-B (290-320 nm)	Photokeratitis	Accelerated aging of the skin Increased pigmentation Immunosuppression Skin burn Skin cancer
UV-A (320-400 nm)	Photochemical cataract	Accelerated aging of the skin Pigment darkening Skin burn
Visible/Near-Infrared (400-1400 nm)	Photochemical and thermal retinal injury	Photosensitive reactions
Infrared (760-100,000 nm)	Aqueous flare Cataract Corneal burn	Skin burn

Fig 3. Eye and skin damage associated with various wavelengths of light.⁵⁶⁻⁵⁸

surgery fellow who allowed his goggles to slip onto his nose.^{63,64}

Risk factors

The eye is widely regarded as the organ that is most sensitive to laser radiation, and nearly all the structures of the eye are susceptible to laser-induced injuries⁴⁷ (Table IV). Retinal injuries that threaten vision vary in severity based on several laser- and eye-related factors, the most important being the duration of exposure, quantity of energy delivered, and locus of injury within the retina.⁶⁵

An important risk factor for development of laser eye injury is the lack of protective eyewear. Particularly vulnerable are tissues that contain pigment, because dermatologic lasers are commonly devised to target specific chromophores, including melanin in the dermal hair follicle. In the anterior segment of the eye, the iris and ciliary body are tissues containing melanin and prone to damage during photoepilation procedures. There is limited pigment in the external eyelids, and therefore these are not an effective shield to block energy emanating from pigment lasers. Instead, if there were exposure related to absent or inadequate shielding, light would penetrate the less pigmented eyelid tissue and be absorbed by the pigment-rich iris.⁶¹

Pathophysiology

Lasers produce a light beam that is coherent, monochromatic, unidirectional, and minimally divergent. Consequently, lasers deliver most of their radiant power to small surface areas⁶⁵ (Fig 3). Thermal damage occurs when energy is absorbed by a suitable chromophore, resulting in heating of the same. An increase in temperature of at least 108°C causes denaturation and coagulation of proteins, resulting in cell death, with ensuing tissue necrosis and scarring. Melanin is the most important pigment in the retina; it absorbs light throughout the visible

Table IV. Variables that affect eye injury*

Variable	Relevance to eye injury
Wavelength	Affects skin absorption and penetration
Exposure duration	Longer duration produces more damage
Pulse duration	Shorter pulse produce more damage
Intensity	More energy produces more damage
Location of injury	Foveal damage is worst; edema and inflammation may cause parafoveal lesions to spread to fovea; and the Bell phenomenon (closing eyes causes upward eye movement, which may relocate the iris to a location where it is vulnerable to injury)
Pupil size	Dilated pupil allows more energy to enter the cornea
Retinal pigmentation	Heavy pigmentation will absorb more laser energy, causing more injury; and absorption is dependent on the amount of absorptive materials in the skin (eg, melanin, hemoglobin, xanthophylls, and water)

*Data from Pierce et al,⁴⁷ Shulman and Bichler,⁶⁰ Barkana and Belkin,⁶⁵ and Dudelzak and Goldberg.⁶⁶

and near-infrared spectrum and is densely concentrated in the retinal pigment epithelial cells and focally in the choroid. It is in these areas that the thermal damage from laser injury is typically greatest and most problematic.⁶⁵

Clinical features

Retinal laser injuries (Fig 4) are often characterized by a sudden loss of vision, often followed by marked improvement over a few weeks, and occasionally by severe late complications.⁶⁵ Other signs and symptoms of laser eye injury include pain or soreness of the eye,⁶¹ pigmentary cells in the chambers of the eye,⁶⁰ synechiae,⁶⁰ oval pupils,^{61,67} reduced visual acuity,^{60,67} and photophobia,^{60,67} either immediately⁶⁷ after laser treatment or a few days later.⁶¹ Exposure to the carbon dioxide laser (10,600 nm) can be detected by a burning pain at the site of exposure on the cornea or sclera. Exposure to laser light in the visible light spectrum stimulates a bright color flash of the emitted wavelength and an after-image of its complementary color (eg, a 532-nm laser would produce a green flash followed by a red after-image). Subsequent retinal damage may result in difficulty in detecting certain (eg, blue or green) colors.

Diagnosis/imaging tests/treatment

Suspected ocular damage (Fig 5) or visual symptoms during laser treatment (eg, photophobia,

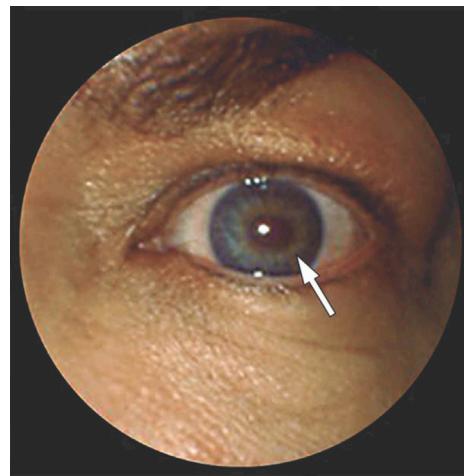


Fig 4. Left eye 1 day post-eyebrow laser photoepilation injury. Note the distortion of the pupil (arrow).⁶¹

pain, or decreased acuity) should result in treatment discontinuation and referral for ophthalmologic examination.⁶⁹

Prevention

It is important that physicians and other health care workers who operate lasers exercise extreme caution in ensuring proper eye protection for themselves and their staff when working with lasers.

Safety standards have been developed for ocular exposure to ultraviolet, visible, and infrared radiation. Standards for the safe use of lasers are provided by the American National Standards Institute.⁶⁵ A warning sign is displayed on the external door of any room in which lasers are used.⁶⁶ Any person who may possibly be exposed to harmful light energy, including the laser operator, support staff, patient, and visitors, must wear appropriate protective eyewear.⁶⁶

Protective eyewear is chosen based on the wavelength of light emitted by the laser. Each pair of laser safety goggles is designated with a central wavelength of rejection, or a rejection band comprised of a range of wavelengths, and the optical density afforded by the lens. The optical density parameter is the log of the attenuation of light transmitted through the lens. The higher the optical density, the greater the protection.^{61,66} Adequate eyewear has an optic density of ≥ 4 for the wavelength of the laser.⁷⁰ Eye shields protect the chromophores within the eye from absorbing monochromatic light from the laser that can damage the eye.⁷¹ Improper preparation, placement, or selection of eye shields may result in failure to stop the transfer of heat from the laser to the eye, causing direct corneal damage.⁷¹ Eye shields can be internal (ie, placed between the globe and eyelid) or external.⁷¹

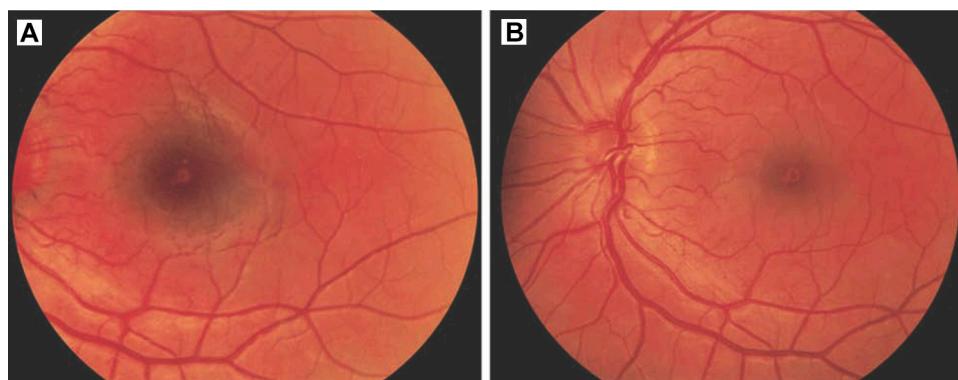


Fig 5. **A**, Four days after a photoepilation accident injuring the eye, there is fovea edema, surrounding subretinal hemorrhage, and several small, hypopigmented retinal pigment epithelium lesions. **B**, One month after the accident, foveal edema and subretinal hemorrhage have resolved, and a small area of foveal retinal pigment epithelium degeneration has developed.⁶⁸

In general, fully opaque shields are used for patients who do not need to see during the procedure. External shields are used routinely. Internal eye shields are generally considered more protective, and are used when procedures are performed very close to the eye, and external shields are therefore impractical. Internal eye shields do not cover the patient's entire eye and may shift with movement, and the operator must ensure that ocular pigmented structures, including the iris, are fully protected at all times. Caution should be exercised with use of internal eye shields, because minor injuries—most commonly corneal abrasions—can occur.⁷¹

Although eye protection is essential, laser eye injury can occur even if protection is used.⁶¹ Goggles and shields can shift during use, and laser light can penetrate through to exposed, unprotected surfaces. It has also been postulated that light can reflect off the cheekbone or orbital rim and enter the eye indirectly.

Treatment

Consultation with an ophthalmologist is imperative for proper assessment and treatment of laser eye injury. Once the dermatologist has made the presumptive diagnosis and transferred the patient to the care of an ophthalmologist, the latter will determine the course of therapy. Current medical therapy for retinal injury is largely limited to use of corticosteroids, with the attendant rationale of reducing the cellular inflammatory response to injury, thereby possibly minimizing its extent.⁶⁵ Benefits of treatment have been variable, and the best results have included complete recovery of vision.⁶⁵ Anecdotal case reports describe the use of therapeutic use of antioxidant vitamins and vasodilator medications.⁶⁵

Surgical management may be considered for removing vitreous and periretinal hemorrhages, but specific treatment protocols are not well established. Typically, hemorrhages resolve spontaneously within a relatively short time, from 2 weeks to a few months.⁶⁵

LOCAL ANESTHETIC AND LIDOCAINE TOXICITY

Key points

- Lidocaine toxicity, although rare, is a reported complication of dermatologic surgery
- Symptoms of lidocaine toxicity vary based on serum lidocaine concentrations
- The maximum safe dose of lidocaine in an adult is 5 mg/kg without epinephrine and 7 mg/kg with epinephrine. If dilute tumescent anesthesia is being used for large procedures, the known safe dose of lidocaine with epinephrine is 55 mg/kg
- If patients experience any of the signs and symptoms associated with excess serum lidocaine, vital signs should be obtained and supplemental oxygen should be administered
- Serious toxicity with central nervous system manifestations should be treated with barbiturates or benzodiazepines, and anticonvulsants can also be used prophylactically

General/incidence

The levels of peak serum lidocaine concentration during dermatologic surgery have generally been found to be safe and well below the levels associated with lidocaine toxicity.⁷² However, lidocaine toxicity, although rare, is a reported complication

Table V. Features and management associated with various plasma lidocaine levels

Lidocaine level, mcg/mL	Symptoms	Management
1-6	Circumoral and digital paresthesia, restlessness, drowsiness, euphoria, and lightheadedness	Observation and oxygen supplementation
6-9	Nausea, vomiting, muscle twitching, tremors, blurred vision, tinnitus, confusion, excitement, and psychosis	Diazepam, airway maintenance, oxygen supplementation, and EMS activation
9-12	Seizures and cardiopulmonary depression	Respiratory support, oxygen supplementation, and EMS activation
>12	Coma and cardiopulmonary arrest	Cardiopulmonary resuscitation and life support, oxygen supplementation, and EMS activation

EMS, Emergency medical services.

of dermatologic surgery. Problems may occur when a patient is given a dose exceeding the safe limit or lidocaine is inadvertently infiltrated directly into the intravascular compartment. Toxicity may result from an overdose of medication, an excessively rapid systemic uptake,^{73,74} impaired hepatic metabolism,⁷⁵ or from drug interactions.⁷⁶

Clinical features

Symptoms of lidocaine toxicity begin at serum lidocaine concentrations of about 1 to 5 µg/mL, with subjective sensory alterations, starting with complaints of dizziness and lightheadedness, followed by tinnitus, circumoral paresthesia, blurred vision, and a metallic taste (Table V). With higher serum concentrations (5-8 µg/mL), nystagmus, slurred speech, localized muscle twitching, and fine tremors may occur. At 8 to 12 µg/mL, focal seizure activity begins and may progress to tonic-clonic seizures, and at even higher concentrations, to respiratory depression, cardiac arrest, and coma.⁷⁷ Among common nonlidocaine local anesthetics, bupivacaine exhibits the smallest therapeutic range, and acutely elevated plasma levels may result in cardiac manifestations that can include ventricular tachyarrhythmias and asystole, even before central nervous system symptoms.⁷⁸ This usually occurs from direct intravascular injection of the anesthetic.

Although guidelines for safe quantities (in grams) of lidocaine injection based on weight of the patient have been described, they do not explicitly stratify the recommended dosage based on the anatomic area to be treated. Absorption of anesthetic will occur more effectively over thin skin and mucosa than on thicker areas, such as acral skin. Local adverse effects of anesthesia infiltration can occur based on vascular compromise secondary to excessive volumes or injection into locations such as the digits. Large volume infiltration of anesthesia into distal digits may lead to necrosis, although this is

unlikely in the absence of tourniquet use or preexisting peripheral vascular disease.⁷⁹ In addition, care should be exercised when using local and topical anesthetics on eyelid skin because ocular damage, including vision loss, has been reported.⁷⁷ Inadvertent globe penetration during eyelid anesthetic injection is an uncommonly reported event primarily described in the ophthalmology literature. Such injuries can entail corneal perforation, traumatic cataract formation, vitreous hemorrhage, retinal tears or detachment, and optic nerve injury.⁸⁰⁻⁸² In addition to needle trauma, chemical irritation to the eyes can occur with anesthesia injections and from topical anesthetic creams applied to the eyelids.^{83,84} Caution must also be exercised when topical anesthetics are used over large surface areas. Improper product use in this context can culminate in dire adverse events. Cardiovascular collapse and even death has been reported because of the application of topical anesthesia under occlusion to the skin before laser treatment; while topical anesthesia is usually safe, application to entire limbs under occlusion is a risky use that, if necessary for the best interests of the patient, should be carefully monitored in a controlled setting.⁸⁵⁻⁸⁷ The mechanism of action of severe toxicity when large areas are treated with topical anesthesia under occlusion is believed to be methemoglobinemia. Anesthesia-related methemoglobinemia may occur even more commonly in infants.⁸⁸⁻⁹⁰

Diagnosis

Diagnosis is predicated upon timely interpretation of the signs and symptoms described above; however, serum concentrations of lidocaine may also be obtained if the physician suspects toxicity. Upon a preliminary diagnosis of anesthetic toxicity, referral to EMS for additional diagnosis and management is appropriate.

Prevention

Staying within known, predetermined safe doses of anesthetic calculated based on body weight is the first step in the prevention of toxicity. Appropriate doses vary based on the specific anesthetic used and the mode of use (ie, intralesional injection, topical application, or tumescent technique), as well as the presence or absence of epinephrine in the mixture. For instance, the maximum safe dose of lidocaine in an adult is 5 mg/kg without epinephrine and 7 mg/kg with epinephrine at standard lidocaine (1-2%) concentrations.⁹¹ In addition, concentrations of dilute lidocaine (0.05-0.1%), referred to as tumescent anesthesia, are safe for subcutaneous injection at 55 mg/kg.⁹¹ In children, the maximum safe dose of lidocaine is 2.0 mg/kg without epinephrine and 4.5 mg/kg with epinephrine per dermatologic surgical sources.⁹² However, according to some other pediatric literature, higher doses of lidocaine can be used (ie, 4.5 mg/kg without epinephrine and 7 mg/kg with epinephrine), but lower doses should be used in highly vascular areas.⁹³ Of note, neonates with jaundice are especially at risk when administering lidocaine because the preservative parabens may potentially displace bilirubin from albumin, thereby worsening the jaundice. As such, some have suggested using preservative-free anesthetic solutions in jaundiced neonates.⁹² Frequent aspiration during injection can minimize the risk of accidental intravascular injection. Minimizing contact of anesthesia to the eye mucosa can help prevent ocular injury. Topical anesthetics are best applied on intact skin rather than inflamed, denuded, eroded, or eczematous areas. Amide topical anesthetics should be avoided or used sparingly in patients with severe liver disease; ester anesthetics should be similarly avoided in patients with pseudocholinesterase deficiency. Limiting use of eutectic mixture of local anesthetics in newborns, particularly those taking methemoglobinemia-inducing agents, may be prudent. Monitoring of the product amount applied, total surface area covered, thickness of stratum corneum, and duration of application can reduce the likelihood of adverse events. For large treatment areas, product application may be restricted to select regions that are most sensitive (ie, "hot spots"). Topical anesthesia may also be supplemented with oral anxiolytics, pain relievers, nerve blocks, direct local anesthesia, and intravenous sedation as appropriate. Ice, refrigerated ultrasonography gels, and air cooling devices (eg, Zimmer Cooling Devices; Zimmer MedizinSystems, Irvine, CA) may increase intraoperative patient comfort and permit the decreased use or elimination of topical anesthetic.

Patient distraction strategies, such as talking to the patient (ie, "talkesthesia"), vibration devices, deep breathing exercises, and provision of stress-squeezing balls may enhance patient comfort during procedures. Vibration in conjunction with verbal distraction was found to be more efficacious than vibration alone,⁹⁴ suggesting that supplementation of anesthesia by combining noninvasive methods may improve pain control and patient comfort. It is recommended that patients ≥ 7 years of age who weigh >20 kg should not have >20 g of eutectic mixture of local anesthetics applied to their skin, with this covering ≤ 200 cm² of surface area for ≤ 4 hours. On the other hand, newborns (<3 months of age) weighing <5 kg should not have >1 g of eutectic mixture of local anesthetics applied to an area ≤ 10 cm² and for <1 hour.⁹⁵ Guidelines for other topical mixtures, such as LMX (Ferndale Laboratories, Ferndale, MI), are distinct, and physicians should refer to manufacturer guidelines for specific recommendations.

Management

The most important step in managing an overdose of anesthetic is the rapid recognition of the toxicity, followed promptly by referral to EMS for additional management. While awaiting the arrival of EMS, if the patient begins to experience any of the signs and symptoms associated with lidocaine (or the particular anesthetic) toxicity, the patient is placed in the supine position. Vital signs are obtained, and supplemental oxygen administered, if available. Any topical anesthetic is washed off immediately. Once EMS arrives, if the patient has lost consciousness, an airway is maintained and ventilation is begun. Serum lidocaine concentration may be obtained and the patient may be given benzodiazepines to treat the central nervous system manifestations (eg, midazolam in 1-mg doses, titrated to effect) or barbiturates (eg, thiopental in 25-mg doses, titrated to effect).⁷⁸ In addition, anticonvulsants may be administered to provide prophylaxis from, or to treat seizures induced by, anesthesia toxicity. Bupivacaine-induced asystole and ventricular tachyarrhythmias may be treated with prolonged CPR (often >1 hour), with bretylium being preferable over lidocaine to correct bupivacaine-induced ventricular tachyarrhythmias.⁹⁶

MOTOR NERVE TRANSECTION

Key points

- **The nerves at greatest risk for injury during cutaneous surgery are the temporal and marginal mandibular branches of the facial nerve and the spinal accessory nerve**

- **The temporal nerve is most susceptible to transection superior to the zygomatic arch and lateral to the lateral eyebrow**
- **Clinical presentation of temporal nerve transection is a flattened forehead, eyebrow ptosis, and an inability to raise the ipsilateral eyebrow**
- **The marginal mandibular nerve is at greatest risk in the neck because of lax and atrophic overlying tissue, and injury can also occur along the jaw margin**
- **Marginal mandibular nerve injury results in an inability to draw the lower lip downward and laterally**
- **The spinal accessory nerve is most susceptible to injury at the Erb point**
- **Injury to the spinal accessory nerve presents with shoulder droop, winged scapula, and loss abduction of the arm**

General/incidence

All muscles of facial expression are innervated by the facial nerve. The facial nerve emerges from the stylomastoid foramen, penetrates the parotid gland, and traverses between its superficial and deep portions. The nerve leaves the mid-parotid gland as it divides into 5 major branches: temporal, zygomatic, buccal, marginal mandibular, and cervical.^{97,98}

The nerves at greatest risk for transection, trauma, ligation or electrical injury during cutaneous surgery are the temporal branch of the facial nerve, which travels superiorly under the zygomatic arch and courses upward superficially under the skin; the marginal mandibular branch of the facial nerve where it crosses over the mandible⁹⁹; and the spinal accessory nerve at the Erb point, the area in the posterior cervical triangle of the neck where it exits the posterior edge of the sternocleidomastoid muscle. Transection of the buccal and zygomatic branches rarely leads to a clinically noticeable deficit because of the robust cross innervation and arborization of the distal portions of these nerves.

The temporal branch of the facial nerve is most susceptible to transection at its most superficial course, superior to the zygomatic arch and lateral to the lateral eyebrow¹⁰⁰ (Fig 6). Cases of nerve transection during cutaneous surgery have been reported in association with resection of large cutaneous tumors in this "danger zone"¹⁰¹; however, the highest incidence of paralysis is after rhytidectomy.¹⁰⁰ It is difficult to determine the incidence of nerve transection because of a limited number of reported cases in the literature. Cases associated with tumor resection may be unavoidable when the tumor is engulfing the nerve trunk.

The temporal branch of the facial nerve travels on the undersurface of the parietotemporal fascia; however, the depth below the skin is not constant because of the varying amount of overlying adipose tissue.¹⁰² The nerve splits into 3 or 4 rami. Fig 6 shows the course of the nerve where it is at greatest risk for transection.

The marginal mandibular nerve is typically found 1 to 2 cm below the lower border of the mandible. However, in elderly patients, the nerve may be present much lower in the neck because of ptosis associated with lax and atrophic tissue.¹⁰⁰ Patients at greatest risk for nerve damage in this area are those with atrophy or hypoplasia of the platysma muscle and skin atrophy. Dissection in this region beneath the platysma muscle can also put the nerve at risk.

The spinal accessory nerve is most susceptible to injury, as noted above, at the Erb point, where the transverse cervical, lesser auricular, and spinal accessory nerves emerge from beneath the posterior border of the sternocleidomastoid muscle. Most commonly, inadvertent transection occurs during procedures in the posterior triangle of the neck, such as radical neck dissection, lymph node dissection, an extensive cervical lift, tumor resection in the area, or even minor procedures, such as obtaining a biopsy specimen or abscess drainage.¹⁰³

Presentation

The presentation of temporal nerve transection is a flattened forehead, eyebrow ptosis, and an inability to raise the eyebrow. This can cause significant functional and cosmetic morbidity. In addition, the resultant eyebrow ptosis and redundant upper eyelid skin can cause upper visual field compromise.¹⁰⁴ Because of the effects of local infiltration of anesthetic, a medication-induced transient paralysis of the brow is common during surgery and a proper assessment of permanent nerve injury cannot be made until the local anesthetic effect has dissipated, which can be hours to a day later. Even so, paralysis of the facial nerve postoperatively is typically transient, with restoration of complete or partial motor function—albeit over ≥ 6 months to 2 years.¹⁰¹ Some authors have estimated that approximately 80% of facial nerve injuries after rhytidectomy will have a spontaneous return of function within 6 months, making a watchful, waiting approach not unreasonable.¹⁰⁰

Palsy of the marginal mandibular nerve results in denervation of the depressors of the mouth (ie, the depressor anguli oris and depressor labii inferioris). Therefore, antagonists to these muscles are able to function unopposed, resulting in an inability to draw the lower lip downward and laterally or to evert the

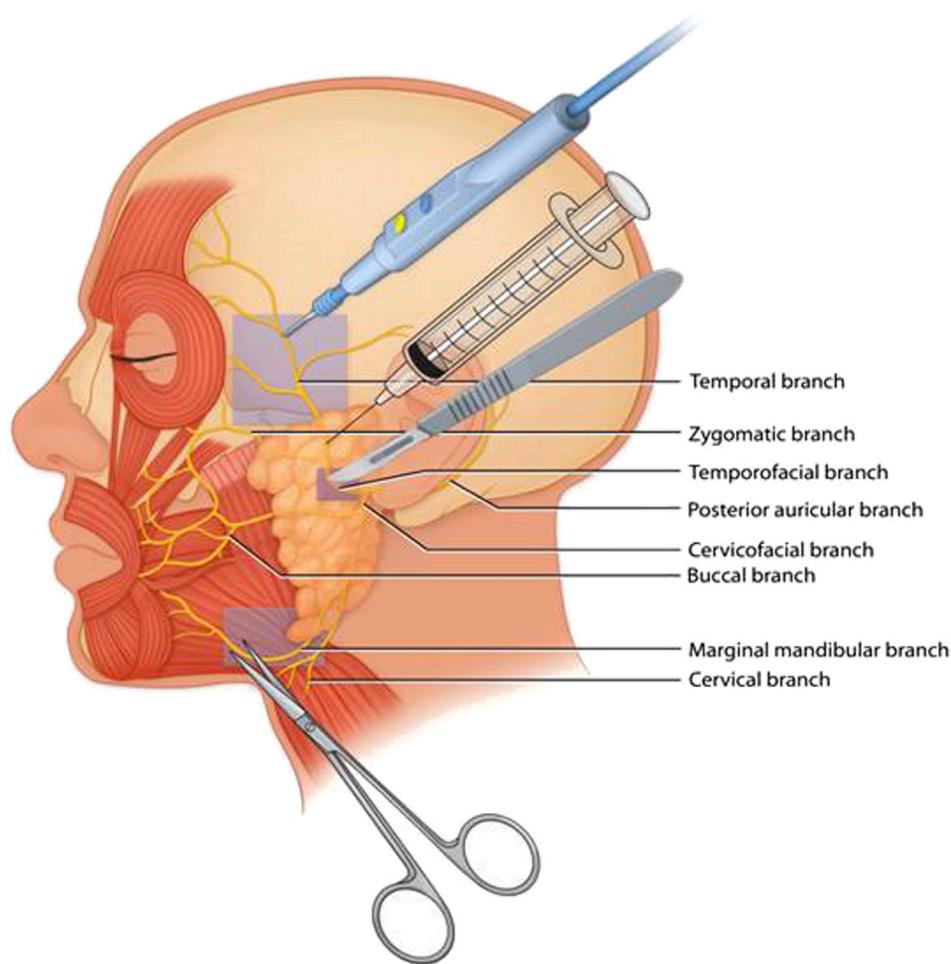


Fig 6. Danger zones for motor nerve transection (shaded areas). Transection usually requires an incisional instrument, such as a scalpel, but temporary nerve palsy may be introduced by overlying blunt dissection, cautery, or needle trauma.

vermillion border on the affected side. The mouth appears normal at rest and the defect becomes evident on smiling.

Injury to the spinal accessory nerve presents with shoulder pain and trapezius muscle palsy that subsequently results in drooping of the shoulder girdle inferiorly and laterally as well as flaring of the wing of the scapula and commonly loss of abduction of the arm.

Management

Treatment options for temporal nerve transection in cases without eventual return of function include nerve reconstruction by a microvascular surgeon. This includes either reapproximation of the severed nerve or placement of a nerve graft.¹⁰⁵ Flynn et al¹⁰¹ recommend marking the ends of the severed nerve with nonabsorbable colored suture in the event that a large facial nerve is severed.

An alternative treatment option is surgical repair of the ptotic brow by unilateral brow lift on the

affected side. This can be achieved by several different repair options, including direct brow-lift, which may entail resection of an ellipse to raise the ipsilateral brow; indirect temporal or coronal brow-lifts; and adjunctive upper lid blepharoplasty.¹⁰⁴ Plastic surgery or otolaryngology may be consulted regarding such interventions.

Management of other types of nerve transection may similarly entail referral to the appropriate surgical specialists. Treatment of marginal mandibular nerve transection is often by conservative management, including exercises, physiotherapy, or other noninvasive methods to keep patients actively engaged in the recovery process. Loss of spinal accessory nerve function also is also usually managed conservatively.

Management of spinal accessory nerve injury includes strengthening of the remaining scapula stabilizers, prevention of trapezius stretch/lengthening, and maintaining the full range of motion of the shoulder girdle. For those that do not respond to this

conservative management, surgical treatment can be attempted with procedures such as dynamic stabilization, which is accomplished by triple transfer of the levator scapulae, rhomboideus major, and rhomboides minor muscles laterally on the scapula.^{103,106}

Damage to motor nerves can occur with surgery proximal to “danger zones” of the head and neck region. Preoperative discussion with the patient before the initiation of dermatologic surgery in vulnerable locations may be helpful. Likewise, a thorough understanding of the anatomy of the head and neck region can help identify the course of critical nerves and the locations in which additional caution is warranted.

RETROBULBAR HEMATOMA

Key points

- **Retrobulbar hematoma can present as a complication of eyelid surgery**
- **Risk factors that increase the risk for postoperative hematoma formation are those associated with bleeding**
- **Pathophysiologic similarity to compartment syndrome, in which pressure causes ischemia and neural damage, has been suggested as a mechanism**
- **Common presentations of retrobulbar hematoma may occur ≤ 24 hours of surgery, but delayed presentations have been observed more than several days later**
- **The management of retrobulbar hematoma is relieving orbital pressure to reestablish normal blood flow**

General/incidence

Retrobulbar hematoma or hemorrhage (RBH) is an ocular emergency that can result in permanent vision loss.¹⁰⁷ With prompt treatment, vision impairment is often reversible.^{108,109} The incidence of orbital hemorrhage associated with cosmetic eyelid surgery is 0.055% (1 in 2000 patients).¹⁰⁷ Permanent vision loss occurs in 0.0045% (1 in 10,000 patients).¹⁰⁷ Blindness after blepharoplasty is a documented complication and can occur because of RBH.¹¹⁰ There have not been any reported cases in dermatology.¹⁰⁷

Risk factors

Certain patient characteristics increase the risk for postoperative RBH. The preoperative examination of patients undergoing blepharoplasty can identify relevant risk factors,¹¹⁰ including hypertension, vascular disease, glaucoma, coagulopathy, or courses of drugs such as nonsteroidal

antiinflammatory drugs, salicylates, or anticoagulants, such as warfarin sodium.¹¹⁰

Pathophysiology

The method by which blindness occurs is complicated and remains unclear.¹¹¹⁻¹¹³ Conceivably, pressure on the neurovascular optic bundle from adjacent hemorrhage can lead to permanent compromise of the essential structures and therefore cause blindness. Incision of the orbital septum and manipulation of orbital fat are likely prerequisites for such outcomes, which tend to develop after extensive postoperative orbital hemorrhage. Hemorrhage within the orbit may be triggered by traction on orbital fat, collect after resection of orbital fat with unidentified intraoperative bleeding, or be a manifestation of posterior extension of wound hemorrhage associated with delayed bleeding in patients with poorly controlled systemic hypertension.¹⁰⁸

Visual loss appears because of an increase in intraocular pressure. Because the globe is enclosed in a continuous cone-shaped facial envelope with rigid bony walls on all sides except anteriorly—where the orbital septum and eyelids form an inflexible boundary—there is little room to accommodate the increase in blood volume if bleeding occurs in this space. Accumulating hemorrhage displaces the globe anteriorly, which appears clinically as proptosis. A resulting compartment syndrome-like effect coincides with decreased perfusion because of increased tissue pressures in the enclosed space.^{111,113} Untreated, irreversible injury¹¹³ occurs as ischemic damage affects the retina or optic nerve.^{107,111,113,114} It has also been postulated that a pressure within a tense orbit may exceed the mean arterial pressure of the ophthalmic artery or central retinal artery, thereby preventing blood flow in the central retinal artery.^{107,108}

Clinical features

Development of orbital hemorrhage is most common ≤ 24 hours after surgery—and especially ≤ 3 hours after surgery—but can occur as late as several days after surgery.¹⁰⁷ Signs and symptoms include pain, proptosis, chemosis, diplopia, subconjunctival ecchymosis, increased intraocular pressure, stony hard eyeball, mydriasis, pressure sensation, decreasing visual acuity, ophthalmoplegia, loss of direct papillary light reflex with preservation of consensual light reflex, loss of vision, diplopia, nausea, and vomiting^{107,111,115,116} (Fig 7).

Diagnosis/imaging tests

Acute orbital hemorrhage is a medical and surgical emergency. The prompt recognition of

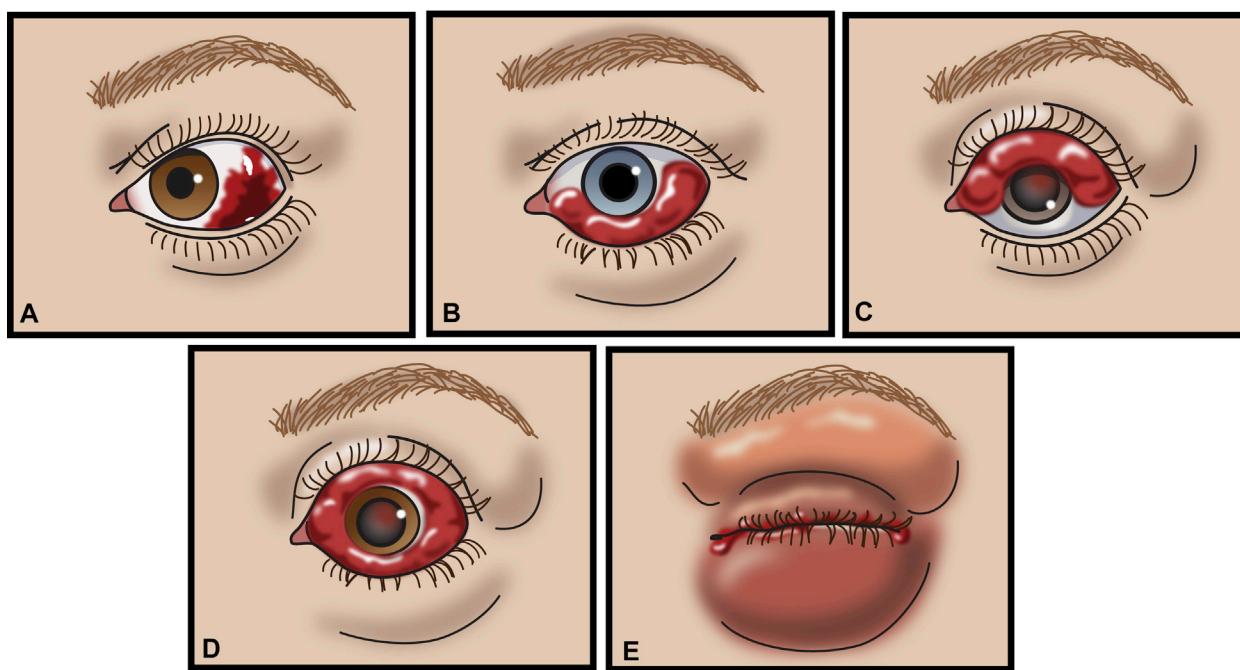


Fig 7. Potential clinical presentations of retrobulbar hematoma (as typically occurring in different patients).¹¹⁶ **A**, Subconjunctival hemorrhage. **B**, Inferior conjunctival chemosis. **C**, Superior conjunctival chemosis. Hemorrhage may displace the globe forward but not sufficiently to produce proptosis. **D**, Orbital proptosis, diffuse subconjunctival hemorrhage, and conjunctival chemosis. **E**, Proptosis and high orbital pressure caused by retrobulbar hemorrhage.

severe postoperative bleeding facilitates timely intervention and the prevention of permanent visual sequelae.^{108,116} The role of the dermatologist is to identify the likely problem, and then to make an immediate referral to ophthalmology for further diagnosis and management.

On the ophthalmology service, the diagnosis can be made clinically, with tonometry or ultrasonography, or may require confirmation with a computed tomography or magnetic resonance imaging scan. A specific finding of all these imaging techniques is the so-called “guitar pick sign”—a conical deformation of the posterior ocular globe, mimicking the shape of a guitar pick^{116,117} (Fig 8). Imaging is typically postponed if there are signs of worsening visual acuity that require immediate therapeutic intervention.¹¹⁶

Prevention

If the patient’s existing medical conditions can predispose to RBH, close postoperative follow-up is appropriate. Thyroid eye disease is frequently associated with increased eyelid vascularity and orbital congestion, which may elevate the risk of periocular hemorrhage.¹⁰⁸ Poorly controlled systemic hypertension or underlying coagulopathies may cause a delay in intraoperative hemostasis and increase the

risk of hematoma formation.¹⁰⁸ Systemic diseases, such as renal disease, that may contribute to altered eyelid positions and eyelid edema should be investigated.^{108,118} Smoking can also potentiate hematomas.¹¹⁸ Optional medications with anticoagulant and cardiovascular effects that may be discontinued before surgery in patients at highest risk include aspirin, nonsteroidal antiinflammatory drugs, low molecular weight heparin products, factor Xa inhibitors, warfarin, large doses of vitamin E, ginkgo biloba extract, garlic, ginseng, kava, ephedra, and other herbal agents.^{108,118} Numerous over the counter medications may have anticoagulant functions.¹¹⁴ Physician-prescribed anticoagulants and cardiovascular drugs are typically not stopped perioperatively.

Intraoperative hemostasis is important when performing eyelid surgery.^{108,114} The use of epinephrine has been a topic of some debate with respect to RBH. Though epinephrine is known to prolong the duration of action of the anesthetic agent and reduce intraoperative bleeding, some believe that epinephrine stimulates vasospasm and rebound congestion after its vasoconstrictive effect wears off.¹⁰⁸ However, in general, epinephrine-containing local anesthetics are commonly used in periocular skin surgery, and they appear to reduce

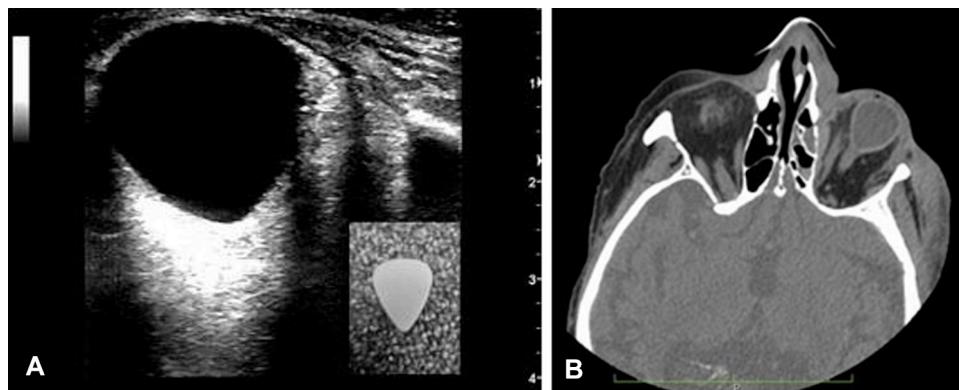


Fig 8. Guitar pick sign. **A**, Ultrasonographic image showing conical deformation of the left posterior ocular globe, mimicking the shape of a guitar pick. **B**, Computed tomography scan of the orbits demonstrating conical deformation of the left posterior ocular globe. Reproduced with permission from Theoret et al.¹¹⁷

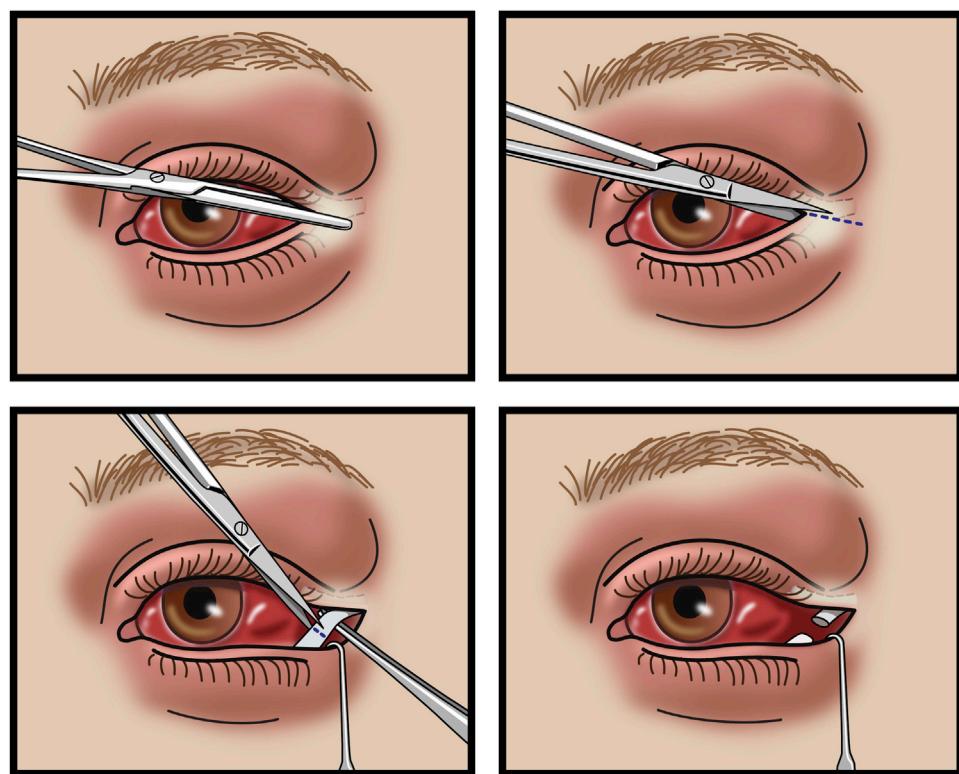


Fig 9. Lateral canthotomy and cantholysis. The treatment of orbital hemorrhage requires relieving orbital pressure to allow normal blood flow to the eye. This is accomplished with a lateral canthotomy and cantholysis to allow the lower lid to be freely mobile.

intraoperative bleeding when accompanied with meticulous cauterization and other hemostatic measures.

Certain postoperative patient instructions may help minimize risk of RBH. Patients are instructed to continue taking their antihypertensive medications and avoid sudden rises in blood pressure, because these have been found to be major risk

factors for early postoperative hemorrhage.¹⁰⁸ Physicians should remain readily available to their patients for ≥ 24 hours after surgery to attend to any symptoms or excessive postoperative bleeding, given that most complications occur within this time frame.¹⁰⁷ The choice of dressing is an area of contention. Although most dermatologic surgeons prefer occlusive dressings to prevent postoperative

edema, some believe the downside of delayed diagnosis of postoperative bleeding outweighs this potential advantage.^{108,114}

Treatment

Ophthalmologic consultation is essential, and should occur without delay once the condition is identified. Additional treatment then occurs under the care of the ophthalmologist receiving the referral. The mainstay of treatment is immediate surgical decompression of the affected orbit.^{108,113,114,116} Colletti et al¹¹⁶ suggest that a RBH should be decompressed within 60 to 120 minutes. A lateral canthotomy and inferior cantholysis can be performed at the bedside under local anesthesia while waiting to bring the patient to the operating room for definitive treatment^{108,113,116} (Fig 9). Inferior cantholysis detaches the inferior crus of the lateral tendon, leading to a completely mobile lower eyelid.^{113,116} If immediate symptom relief is not seen, further exploration of the orbit may be needed to find the bleeding source and evacuate the hematoma.^{108,116} In this case, ophthalmologic consultation is even more desirable.

Medical interventions can be used as the primary treatment in select cases, or as an adjunctive therapy to complement more definitive surgical management.¹¹⁴ If the intraocular pressure is elevated, topical and systemic glaucoma medications may provide some relief and bring down the pressure. Systemic corticosteroids can be used to improve significant edema.^{113,114} Carbonic anhydrase inhibitors (eg, acetazolamide 500 mg), intravenous corticosteroids, and a rapid infusion of mannitol 20% are a frequently used combination approach.¹¹³ Other nonsurgical treatment methods include the application of topical timolol maleate eye drops (0.25% solution).¹¹³

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Granuloma annulare



Clinical and histologic variants, epidemiology, and genetics

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Learning objectives

After completing this learning activity, the learner should be able to recognize history, pathogenesis, genetics, epidemiology, clinical and histological presentation of GA.

Disclosures

Editors

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Granuloma annulare (GA) is a poorly understood condition characterized by a set of clinical morphologic variants with 2 predominant histopathologic patterns of inflammation. This review provides a comprehensive overview of the available information about the clinical variants and histopathologic features, current epidemiologic data, and potential genetic underpinnings of GA. Much of the current understanding of GA is based on retrospective studies, case series, and case reports; this review aims to synthesize the available information and present it clearly for practicing dermatologists. (*J Am Acad Dermatol* 2016;75:457-65.)

Key words: annular elastolytic giant cell granuloma; granuloma annulare; granulomatous dermatitis.

Granuloma annulare (GA) is a relatively common skin disorder of uncertain etiology. Thomas Colcott Fox first described the entity in 1895 as “ringed eruption,” and over the next decade additional similar reports were described. In 1902, Radcliffe Crocker used the term GA, and a review by Graham Little in 1908 described previous cases of the entity under this name, which became the standard term describing this condition.¹ Over the past century, many case reports and small studies have been published further characterizing different aspects of this condition. While the cause

remains unknown, HIV, diabetes, dyslipidemia, malignancies, thyroid disease, and other conditions have all been described as potentially connected to GA with varying levels of evidence. GA is often localized to the hands and feet, is minimally symptomatic, and frequently self-resolves. However, because of the appearance, tendency to recur, and occasional widespread presentation, patients often desire treatment. While there are many treatment options, limited data are available to guide clinical management. This review will serve to describe the clinical and histologic features of the different

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Fig 1. Localized granuloma annulare. Erythematous annular plaques may be singular (**A**) or multiple (**B**). Localized granuloma annulare may also present as papules coalescing into circular plaques (**C**).

subtypes of GA and to describe available data on the epidemiology, genetics, pathogenesis, disease associations, triggers, and treatment options.

CLINICAL VARIANTS

The term GA appropriately describes the classic variant characterized by ringed erythematous plaques with granulomatous inflammation seen histologically. However, GA now encompasses a spectrum of disease. The most common variant of GA is localized GA (LGA), and other well defined forms include generalized GA (GGA) and subcutaneous GA (SGA). Over time, clinicians have described more atypical, rare variants. These descriptions are frequently presented as isolated case reports or small case series, making a synthesis of the clinical morphologic variants a challenge. Nevertheless, this section will work to clarify the different subtypes and clinical variants of GA.

LGA is the prototypical subtype of GA, and is characterized by pink to red nonscaly papules and plaques often in an annular configuration on the extremities. The hands and feet in particular are commonly involved (Fig 1).²⁻⁴ This subtype is often cited as characterizing around 75% of the reported cases of GA, and has a tendency to remit within 2 years.^{2,3,5-7}

In 1989, Winkelmann published a study of 100 cases of patients with GGA.⁸ This represents one of the largest series of patients with this entity, and is quite helpful in describing the clinical pattern and morphology. Generalized GA was defined as “affecting at least the trunk and either upper or lower, or both, extremities” (Fig 2). Patients were divided into 2 morphologic groups: 67 patients with predominately annular lesions comprised of individual coalescing papules arranged in ring-like configurations, and 33 patients with predominately

nonannular lesions consisting of symmetrically scattered, often coalescing papules favoring the chest and back (Fig 3). Over time, many published reports of GA have described patients’ eruptions as “generalized GA” without strictly adhering to the definition used by Winkelmann in his report. This lack of consistency among subsequent reports of “generalized GA” makes analysis of the available data difficult. Adding further confusion to the literature is the term “disseminated GA.” In their 1989 paper on GGA, Winkelmann and Dabski⁸ rejected 15 cases of patients with extensive involvement of the extremities only, considering them “disseminated, but not truly generalized.” This seems to be an informal use of the English word “disseminated,” rather than Winkelmann’s consideration of “disseminated GA” as a separate and distinct variant of GA. Unfortunately, this term has subsequently been used loosely in the literature, ranging from case reports seemingly using disseminated to mean the same as generalized^{3,9-11} or as a description of cases characterized by nonannular papules (which Winkelmann had considered in his original definition of GGA).⁶ Given the confusion since Winkelmann’s 1989 paper, GA with extensive involvement of the extremities is likely better considered a form of generalized GA rather than its own subtype. Additional studies would need to be conducted to determine whether this difference has any clinical significance, which might justify use of both disseminated and generalized in describing GA.

A particularly noteworthy subtype of granuloma annulare is the subcutaneous variant (SGA). Painless, firm subcutaneous nodules characterize this entity, also known as pseudorheumatoid nodule. SGA is seen nearly exclusively in children, often on the lower extremities (Fig 4), although cases with



Fig 2. Generalized granuloma annulare. Patients may present with annular plaques on the trunk (**A**) and extremities (**B**).

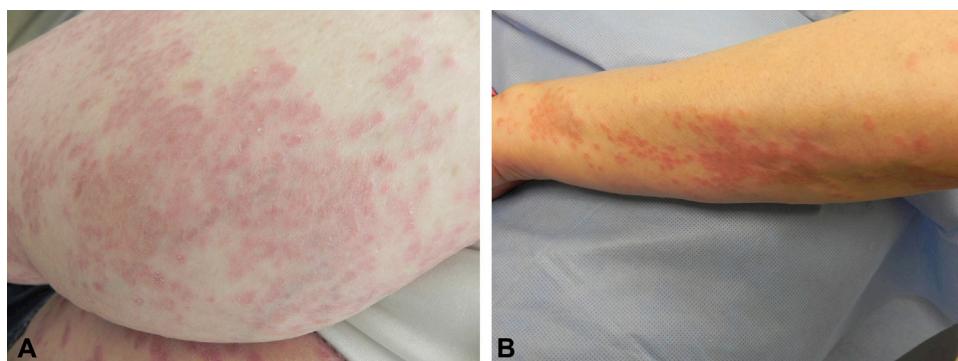


Fig 3. Generalized granuloma annulare with disseminated papules coalescing into plaques on the posterior arm of one patient (**A**) and forearm of another (**B**). Photograph **A** courtesy of Dr Kathy Schwarzenberger.

forehead and scalp involvement have also published. Similar to the other subtypes of GA, the lesions show a tendency to regress with time but may recur.¹²⁻¹⁹

While LGA, GGA, and SGA are the most widely recognized clinical phenotypes of GA, a number of rare variants have been reported. Of these less common forms, perforating GA (PGA) is perhaps the best described. PGA seems to have been first reported in 1971, and can present either localized to the extremities or generalized to involve the trunk and extremities.²⁰ The primary lesion in most reports is an umbilicated papule with a central crust or hyperkeratotic core (Fig 5).²⁰⁻²⁴ The lesions may become pustular²⁵ or ulcerate.²⁶ Large flat patches of GA have also been reported^{27,28} ("patch" or occasionally "macular" GA), but given the overlap between this condition and reactive granulomatous eruptions, such as interstitial granulomatous dermatitis, it may be challenging to distinguish between these 2 entities. Extremely rarely reported

variants of GA include palmoplantar, blaschkolinear, pustular, and visceral.²⁷⁻³⁸ In addition, depending on the author, annular elastolytic giant cell granuloma (AEGCG), also known as actinic granuloma, may^{30,39} or may not⁴⁰ represent a photoinduced subtype of GA, or simply GA appearing on sun-damaged skin (Fig 6). One case of GGA on predominately photoexposed areas resolved with features of anetoderma after 5 to 6 months.⁴¹ Descriptions of the clinical variants of GA appear in Table I.

EPIDEMIOLOGY

There have been no large-scale, population-based studies documenting the overall incidence or prevalence of GA, although 1 review article published in 1980 reported that 0.1% to 0.4% of new patients presenting to dermatologists were diagnosed with GA.² Overall, the condition is most commonly reported in patients in the first 3 to 5 decades of life, with a female to male ratio of around 1:2:1.^{2,6,7,42-45} However, it is important to



Fig 4. Subcutaneous granuloma annulare is more common in children and presents as a firm, painless nodule. Photograph courtesy of Dr Melinda Jen.



Fig 5. Perforating granuloma annulare is a rare subtype and can present with umbilicated papules with central plugs of keratinaceous material. Photograph courtesy of Dr William D. James.

note that by not differentiating between clinical variants of GA, these data may be skewed, because SGA tends to occur more commonly in children,^{12,14-18} while GGA is often reported in elderly patients.^{8,46,47} One study of Korean patients presenting with GGA described a bimodal distribution in age (44% presented within the first decade of life, and 44% presented over the fifth decade of life).⁴⁴ This bimodal age distribution of GGA has been reported before,² but is not always replicated.

As noted above, SGA is reported almost exclusively in children, with an age range of around 1 to 14 years of age.^{12,14-18} One patient was reported as having lesions present at birth.¹³ PGA has been reported to be more common in children,^{22,23} but it may also affect adults.^{20,21,25,48} Patch GA is typically



Fig 6. Annular elastolytic giant cell granuloma is considered by some a distinct entity, but shares some clinical and histologic features of granuloma annulare. Annular elastolytic giant cell granuloma typically presents with photoexposed annular plaques with central pallor and atrophy.

described in women between 40 and 74 years of age.^{27,28,49}

GENETICS

A relative paucity of data exists on the genetics of GA. In 1987, Winkelmann reported that there were <20 cases of GA described in at least 2 immediate family members.⁵⁰ An additional familial case of generalized PGA was reported 1 year later.⁵¹ GGA and human leukocyte antigen (HLA)-Bw35 may have an association.⁵² HLA-Bw35 has also been associated with thyroid disease,⁵³ which is in itself reported to be associated with GA.⁵⁴ Further evidence for a familial association comes from the first published report of adalimumab use in GA, a 67-year-old woman with disseminated (based on the authors' description, this seems consistent with generalized) GA received 40 mg of adalimumab per week for 3 months with marked improvement in her disease. After her identical twin sister experienced similar results, the patients were found to harbor the HLA-AH8.1 genotype, which has been associated with increased production of tumor necrosis factor-alfa by peripheral blood mononuclear cells.⁵⁵

HISTOLOGY

Histologically, mucin coupled with a palisading or interstitial pattern of granulomatous inflammation represents the principal finding in all subtypes of GA, but other patterns may rarely be seen.^{4,56-61} The palisading pattern is characterized by a central zone of necrobiotic collagen surrounded by palisading histiocytes and varying numbers of lymphocytes (Fig 7). The interstitial pattern is characterized by collections of histiocytes scattered between and

Table I. Clinical variants of granuloma annulare

Type	Classic description	Estimated frequency	Note
Common			
Localized	Annular plaques, limited, classically on the hands or feet	+++++	Most common and well-recognized form of GA
Generalized	Annular plaques or papules, diffuse, classically on the extremities and trunk	++	Extensive involvement of the extremities probably fits into this subtype, and given the confusion in the literature, "disseminated" GA is likely best thought of as a form of GGA in the absence of better data
Subcutaneous	Subcutaneous nodules	++	Almost exclusively seen in children
Uncommon			
Perforating	Umbilicated papules with keratotic core	+	May be more common than reported given the difficulty of histologically locating the area of perforation. Probably associated with HIV, especially when disseminated
AEGCG	Sun-exposed lesions, atrophic white center	+	Considered by some to represent a distinct entity, AEGCG shares many overlapping clinical and histologic features with GA
Patch	Red-brown or violaceous patches, extremities > trunk	+	Can be localized or generalized. There have been few reports in the literature, but almost exclusively described in women
Palmoplantar	Acral papules	Rare	Typically painful, and more often seen on the palms

AEGCG, Annular elastolytic giant cell granuloma; GA, granuloma annulare; GGA, generalized granuloma annulare.

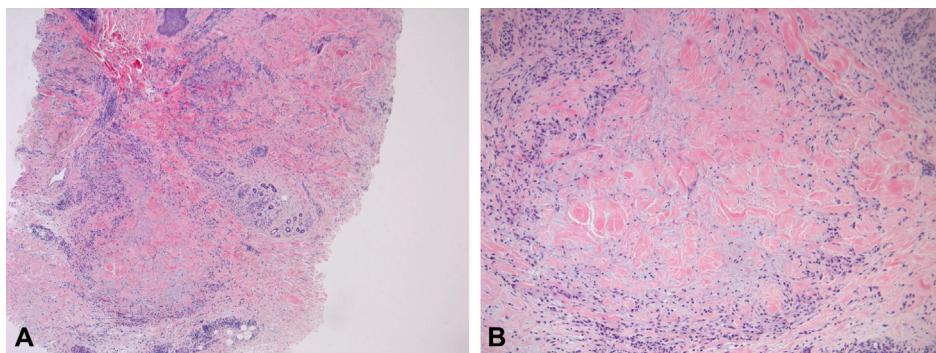


Fig 7. **A** and **B**, Palisading granuloma annulare. Lymphohistiocytic inflammation surrounds central altered collagen with palisades of histiocytes. Mucin is prominent. (Hematoxylin–eosin stain; original magnification: **A**, $\times 40$; **B**, $\times 100$).

around collagen bundles and blood vessels in the papillary and mid dermis (Fig 8). A recent study of 35 cases of GA described these 2 patterns in addition to sarcoidal granulomas and a mixed variant, although correlation with clinical morphology was lacking.⁵⁸ Winkelmann characterized 207 cases of GA and found that 71% showed the interstitial pattern, while 26% showed palisading granulomas.⁶² This study also described mononuclear perivascular inflammation in all cases, and upon electron microscopy revealed histiocytic and macrophagic vasculopathy with small-vessel degeneration in areas of well-developed GA.⁶² Multiple clinical and

histologic morphologies in the same patient have also been described.⁶¹

While many studies group all clinical variants of GA together,⁵⁶ a paper by Yun et al⁴⁴ studied 54 patients in Korea with GGA using the clinical definition put forth by Winkelmann. They found that the 2 predominate histologic patterns were nearly equal in numbers (52% were characterized as palisading; 48% were characterized as interstitial). Mucin was seen in 94% of cases, an eosinophilic infiltrate in 44%, and nuclear dust in 33%. No vasculitis was seen. In 1 paper comparing GGA with LGA, only minor differences were seen on

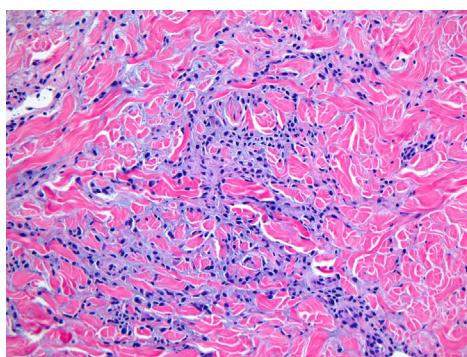


Fig 8. Interstitial granuloma annulare. Histiocytes intercalate between the collagen bundles singularly or in small aggregates. Mucin is again a prominent feature. Distinguishing interstitial granuloma annulare from reactive granulomatous processes, such as interstitial granulomatous dermatitis, may be challenging. (Hematoxylin–eosin stain; original magnification: $\times 100$).

histologic examination, and no specific findings to allow for a diagnosis of GGA versus LGA based solely on histology were found.⁴

The typical findings seen in patients with SGA consist of multiple nodules in the subcutaneous layer and reticular dermis with degenerated collagen surrounded by palisading histiocytes and a peripheral zone of lymphocytes. Mucin is also seen in these deeper lesions.¹²⁻¹⁹ Occasionally, histiocytes are more dispersed in the reticular dermis and subcutaneous layer, without the classic palisading pattern.¹⁶ SGA in particular can mimic sarcoidosis clinically, and the presence of sarcoidal (or epithelioid) nodules histologically can make the diagnosis particularly difficult.⁶¹ Eosinophils can be seen, and may be more common in SGA than in other variants of GA.¹⁷ A comparison of LGA and SGA showed classic palisading granulomas in all cases (13 LGA and 8 SGA).⁶⁰

Perforating GA is characterized by mucinous collagen degeneration surrounded by palisading granulomas, with transepithelial elimination of altered collagen.^{20,22,23,25} This entity may be more common than is reported, given that transepidermal elimination of collagen may be missed without careful examination of serial histologic sections.^{21,22} Histologic findings in the patients with patch GA described by Mutusim and Bridges²⁷ were consistent with the interstitial pattern of GA.

Other granulomatous disorders can mimic GA histologically. Necrobiosis lipoidica (NL) in particular can appear similar to GA under the microscope, because both entities are characterized by altered collagen. Despite this, the simultaneous occurrence of NL and GA is only rarely reported.^{63,64} Several studies have been designed to differentiate

between these conditions, including a 1986 study that showed 12 of 13 cases of GGA and 15 of 32 cases of LGA had intracellular elastin noted on hematoxylin–eosin staining, as opposed to 0 of 20 cases of NL.⁶⁵ Lysozyme staining has been reported as present in lesions of GA as opposed to NL and rheumatoid nodules (RN), which may also be confused with GA histologically.⁶⁶ The monoclonal antibody PG-M1 (a member of the CD-68 cluster) has been suggested as a reliable marker of histiocytes in lesions of GA, though more recently CD-123 staining was found to be denser in lesions of GA than RN or NL. This suggests a greater role for plasmacytoid dendritic cells in GA than previously thought.^{67,68} A novel immunohistochemical stain for adipophilin has been shown to be a potentially useful marker for distinguishing GA, NL, and sarcoidosis. Staining for this marker in GA showed patterns corresponding to the distribution of histiocytes, with both intracellular and extracellular staining. Interstitial GA demonstrated more focal adipophilin expression than cases of palisaded GA.⁶⁹ GA and other granulomatous conditions, including NL and sarcoidosis, have been shown to have strong positivity for *gli-1*, which has been suggested as a potential target for therapeutic inhibition in patients with these conditions.⁷⁰ Other reactive granulomatous dermatoses, such as palisading neutrophilic and granulomatous dermatitis (PNGD), interstitial granulomatous dermatitis (IGD), interstitial granulomatous drug reaction (IGDR), and sarcoidosis can also mimic GA, and the characteristics that may distinguish these entities are described in Table II.

AEGCG shares significant clinical and histologic overlap with GA. While it may best be thought of as a variant of GA, AEGCG is felt by some to be a distinct entity. The histology of AEGCG demonstrates a nonpalisading granulomatous infiltrate of histiocytes, foreign body–type multinucleated giant cells, and lymphocytes in the mid to papillary dermis. Altered collagen, mucin, and lipid deposition are often absent.⁷¹ Elastophagocytosis can be seen, characterized by elastic fibers highlighted within giant cells. Given that GA may also show elastophagocytosis and elastic fiber reduction,^{4,65} that histologic feature alone may not reliably distinguish the 2 entities.

In conclusion, this review has discussed the historical context of GA, provided an overview of the different clinical and histologic subtypes of GA, and discussed the relatively limited data on the epidemiology and genetics of the condition. The accompanying continuing medical education article addresses the pathogenesis, disease associations and

Table II. Histopathologic comparison of the most common presentations of granuloma annulare, palisaded neutrophilic and granulomatous dermatitis, interstitial granulomatous dermatitis, and annular elastolytic giant cell granuloma

	GA	PNGD	IGD	AEGCG
Classic morphology	Annular plaques on the dorsal surfaces of the hands and feet	Palpules on the elbows	Palpable cords on the trunk	Photodistributed annular plaques with atrophic centers

Histology

Palisading variant—central zone of altered homogenized collagen with mucin, surrounded by palisaded histiocytes and varying numbers of lymphocytes and neutrophils; interstitial variant—aggregates of histiocytes intercalating between and around collagen bundles with interstitial mucin

Varies by chronicity. Intense neutrophilic inflammation, with or without signs of leukocytoclasia and vasculitis, altered collagen, sparse palisades of histiocytes, and small granulomas. Mucin is minimal to absent

Scattered interstitial histiocytes in small aggregates with rare giant cells, often surrounding "rosettes" of altered collagen, which may be "detached" and "floating." Vasculitis is absent. Mucin is minimal to absent

Histiocytes grouped in aggregates and small granulomas around altered connective tissue. Elastophagocytosis may be evident on routine histologic sections or special stains. Elastic fibers are reduced or absent on special stains. Mucin is minimal to absent

AEGCG, Annular elastolytic giant cell granuloma; GA, granuloma annulare; IGD, interstitial granulomatous dermatitis; PNGD, palisaded neutrophilic and granulomatous dermatitis.

triggers, and potential therapeutic options for patients with GA.

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Granuloma annulare



Pathogenesis, disease associations and triggers, and therapeutic options

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Learning objectives

After completing this learning activity, the learner should be able to review the systemic workup, disease associations, triggers (medications and others) of GA, and present a review of the available treatments (and evidence supporting each) and a proposed list of labs to check, studies to order, and an algorithm of treatment for GA.

Disclosures

Editors

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Granuloma annulare (GA) represents a cutaneous reaction pattern of unknown cause with a variety of previously described potential disease associations and triggers. This review attempts to synthesize the available data regarding potential etiopathogenesis, reviews the available data on potential GA disease associations and work-up indicated for patients with GA, and discusses potential inciting triggers. In the final part, this article describes the available treatments options and supporting data, and provides a framework for approaching management of patients with GA. The previous accompanying article provided a comprehensive overview of the available information known about the clinical variants, epidemiology, genetics, and histology of GA. (J Am Acad Dermatol 2016;75:467-79.)

Key words: annular elastolytic giant cell granuloma; granuloma annulare; granulomatous dermatitis.

PATHOGENESIS

The pathogenesis of granuloma annulare (GA) is unknown. There have been a number of hypotheses regarding the underlying etiology of GA; however, most of these hypotheses are supported by relatively limited evidence. In a 1977 study, Dahl et al¹ reasoned that because lesions of GA often show blood vessel thickening, occlusion or other damage to blood vessels ultimately may be responsible for the development of GA. To test this, 58 specimens

from patients with GA were studied, and the authors found that immunoglobulin M (IgM), complement, and fibrinogen were present in blood vessels in areas of GA. This led the authors to postulate that the underlying mechanism behind GA is an immune-mediated, type III reaction leading to chronic vasculitis.¹ A similar hypothesis has been suggested for necrobiosis lipoidica (NL),² and both conditions may be associated with diabetes and microvascular damage. In addition, an ultrastructural study of

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patients with localized GA (LGA) and generalized GA (GGA) found that in 4 patients, masses of intercellular fibrin and thickened basal lamina around capillaries was seen more commonly in lesions of patients with GGA.³

Contemporaneously with the Dahl et al,¹ Umbert et al⁴ proposed an alternative mechanism. They postulated that cell-mediated immunity underlies the pathogenesis of GA, based on their data that lymphokines, including macrophage-inhibiting factor (MIF), lead to sequestration of macrophages and histiocytes in the dermis. Upon lysosomal enzyme release by these sequestered cells, connective tissue damage results, which culminates in GA.⁴ In a further study, the same authors found that activation of macrophages and fibroblasts are involved in the pathogenesis of GA, and postulated that their findings showing fibrin and rare IgM and C3 deposition around vessels did not suggest an immune-complex mediated disease, but more likely delayed-type hypersensitivity with secondary tissue and vessel changes.⁵ Ten biopsy specimens obtained from patients with early LGA lesions in a separate study had negative findings on direct immunofluorescence, further suggesting that immune-complex deposition is not the primary process leading to GA.⁶

While the etiopathogenesis of GA is not known, there are multiple studies that lend some additional support to the hypothesis that GA may be triggered by delayed hypersensitivity. In a study of 8 skin samples obtained from patients with GA, the infiltrate was comprised primarily of helper T cells, leading the authors to hypothesize that through interaction with histiocytes, these helper T cells lead to granuloma formation and GA.⁷ A 1999 study⁸ showed that large numbers of T cells in lesions of GA were CD3⁺ and expressed receptors for interferon gamma. In addition, the authors noted that macrophages were differentiated to aggressive effector cells expressing tumor necrosis factor-alfa (TNF- α) and matrix metalloproteinases, which could contribute to the underlying tissue destruction and inflammation.⁸ Active collagen synthesis in lesions of GA has been shown by Northern and in situ hybridization studies. In this paper, the authors showed a low level of transforming growth factor-beta, and elevation in interleukin-1 (IL-1) and -2 (IL-2) receptors, leading them to postulate that collagen synthesis is ultimately regulated by helper T cells through the activation of macrophages and subsequent secretion of fibroblast-activating chemokines.⁹ They postulate that this collagen synthesis is important as a reparative phenomenon in patients with GA. Local production of IL-2 has also

been shown in lesions of GA, and was not found in peripheral blood mononuclear cells.¹⁰

Additional studies that may shed some light on the pathogenesis of GA have been conducted. One study of neutrophil migration found that neutrophil chemotaxis was impaired in the body of GA patients, while normal in vitro.¹¹ The authors hypothesized that in patients with defective neutrophil chemotaxis, macrophages take over their role at an inflammatory site, leading to the granulomatous inflammation seen in GA, rather than suppurative neutrophilic inflammation.¹¹ Eosinophils, though occasionally identified in lesions of GA, are more likely bystanders than actively involved in etiopathogenesis.¹² Heparan sulfate (HS) is normally attached to the surface of keratinocytes, but has been shown to be present in the interstitium in patients with GA.¹³ Elevated levels of serum lysozyme were found in patients with GGA as opposed to LGA and normal controls.¹⁴ TIMP metallopeptidase inhibitor 1 (collagenase) mRNA has been shown to be elevated at the outer edges of palisaded granulomas in patients with GA.¹⁵ The overall significance of these findings in the pathogenesis of GA is unknown, and additional studies are clearly needed.

Some argue that elastic fiber degeneration is the underlying dermal alteration in GA and not collagen, based on electron microscopy results and special studies for elastic fibers.^{16,17} Macrophage metalloelastase (a matrix metalloproteinase) has been shown to be elevated in areas of elastin degradation in several granulomatous conditions, including GA.¹⁸ GA-related elastic fiber destruction has also been reported to culminate in mid-dermal elastolysis.¹⁹ These findings may hint at a common thread between GA and annular elastolytic giant cell granuloma (AEGCG).

An infectious etiology has been postulated; however, studies to date have largely been negative.²⁰ While some infectious agents, including HIV, infectious hepatitis, and *Borrelia* species have been reported as triggers in some cases, the occurrence of GA may represent a non-specific cutaneous reaction in these patients rather than a direct result of the infection. A further discussion of infectious triggers of GA can be found below.

Overall, at least some variants of GA may be ultimately caused by a delayed-type hypersensitivity to an as yet unknown source. Perhaps, given the multitude of reported triggers, associations, and presentations, it is possible that there is no one, singular “cause” of GA but rather multiple pathways that ultimately culminate in this condition.²¹ The reported triggers and multiple diseases reported to be associated with GA are discussed below.

ASSOCIATIONS

GA may occur as an isolated, idiopathic entity, but reports persist describing GA in the setting of a variety of systemic processes. The most widely reported diseases associated with GA are diabetes and hyperlipidemia, though rare reports have also described GA in the setting of malignancies, systemic infections, and thyroid disease. There are also numerous reports of drug-induced forms of GA.

The story of GA and diabetes has evolved over many decades, with numerous papers both supporting²²⁻²⁹ and refuting³⁰⁻³³ a connection between the 2 conditions. In a 1989 paper by Winkelmann et al,³⁴ 20% of patients with GGA were diagnosed with diabetes mellitus. An important caveat noted in this paper also applies to many studies that came both before and after: "A preselected population of more difficult cases seen at tertiary referral institutions ... represents a fraction of the entire group with a given disorder and yields epidemiologically skewed inferences about associations between diseases."³⁴ With that important caveat, there are a number of studies—mostly from large institutions—suggesting an association between GA and diabetes. In 1984, a study of 557 patients with GA found that 24 (4%) had diabetes.²⁶ In a comprehensive study of GA in a Korean population, 4 of 52 patients with GA were found to have diabetes (8%), a higher rate than that of the general Korean population.³⁵ A retrospective case-control study of 61 patients later showed that insulin-dependent diabetes was significantly increased in patients with GA, and the authors noted a higher prevalence of diabetes mellitus (DM) in patients with LGA versus GGA.²⁸ Twelve of 84 patients (14%) with GA were found to have diabetes in 1 paper, with 5 having generalized GA.²⁹ In a study of 52 patients with GA (13 with GGA and 39 with LGA), patients with LGA had similar rates of carbohydrate intolerance as controls, but a significantly higher percentage of patients with GGA (77%) had carbohydrate intolerance.²³ Lending some strength to the reported association between GA and DM, diabetes has been reported in association with other cutaneous reactive granulomatous processes, most notably NL.³⁶

Some reports also describe a lack of association between GA and DM. In a study of 126 patients with GA, no association was found between GA and DM when compared to controls.³¹ Controls were patients with psoriasis, which is now thought to have a potential connection to DM.³⁷ No significant difference between 16 patients with GA and matched controls was found when using several markers of glucose tolerance.³² In another report of 23 patients with LGA or GGA, only 1 patient was diagnosed with

DM.³⁰ There are also 2 separate studies from India that looked at the cutaneous manifestations of 500 patients with type I diabetes³⁸ and 500 patients with predominately type II diabetes,³⁹ and only 1 patient in each study (0.2%) was found to have GA.

In the end, despite a large number of studies published on GA and DM, definitive evidence for an association is lacking. Future studies attempting to connect DM to GA must be well designed and controlled, as the aforementioned studies often used different methods of assessing for diabetes, often did not differentiate between clinical variants of GA (or used different definitions of GA subtypes), or did not assess for likely confounders, including age and comorbidities. Screening is inexpensive; in patients with risk factors or symptoms suggesting glucose intolerance, physicians should consider testing.

In addition to DM, several other conditions have been suggested to be associated with GA. A recent study of 140 patients showed that 80% had dyslipidemia, as compared to about 52% of controls.⁴⁰ Improvement of dyslipidemia led to concurrent improvement of GGA in a 62-year-old Japanese woman, though there could have been other reasons for her improvement.⁴¹ Autoimmune thyroiditis also may be associated with GA, based on small studies and series.⁴²⁻⁴⁴ GA, type I DM, and autoimmune thyroiditis have been reported in the same patient.⁴⁵ Other granulomatous conditions have been described in association with thyroid disease, suggesting that GA and thyroid disease may be related in some patients.^{46,47}

It has been postulated that GA may be associated with an infectious agent, but studies have been mixed. A small study of 10 patients did not reveal any molecular or culture-based evidence for a bacterial, mycobacterial, or fungal cause.²⁰ A similar study looking for *Bartonella* species in 18 cases of previously diagnosed GA also yielded negative results.⁴⁸ A number of European studies have suggested a connection between GA and *Borrelia* species. In one such study, patients with GA were more likely than controls to have detectable levels of *Borrelia burgdorferi* DNA in their urine.⁴⁹ Another study showed that 127 of 157 patients with GA had evidence of *Borrelia* by focus-floating microscopy.⁵⁰ A third study found that pseudorosettes are a common finding in patients with GA, and may be predictive of borrelial infection in European patients with GA.⁵¹ In 2002, Winkelmann²¹ presented a case of tuberculosis (Tb) in which the patient also had GA (based on a polymerase chain reaction study of a lesion that was negative for *Mycobacterium tuberculosis*). The author postulated that historical

cases of GA attributed to Tb were noninfectious, but represented a Tb-related immune response manifesting as GA.²¹ It is worth noting that tuberculoid or granulomatous reactions to tuberculosis infection may mimic GA. Viruses have also been suggested as associated with GA, and a case of GGA in a patient with chronic hepatitis C virus improved after interferon-alfa therapy.⁵² Similarly, a case of GGA in a patient with chronic hepatitis B virus infection also improved after interferon-alfa therapy; polymerase chain reaction studies performed on lesional skin biopsy specimens from this patient were positive for hepatitis B virus DNA.⁵³

Hypothesizing that patients with GA are at risk of developing “odd sequelae,” Dahl⁵⁴ studied 32 patients seen at the Mayo Clinic and found that after at least 20 years of follow-up, most patients with GA heal, remain “remarkably healthy, and do not ordinarily develop other odd diseases.” A recent study found no association between GA and uveitis (in contrast to a previous report⁵⁵), and screening eye examination is not routinely recommended for asymptomatic patients with GA.⁵⁶ GA has also been reported in the settings of sarcoidosis^{57,58} and Sweet syndrome.⁵⁹

GA has been reported in temporal association with various malignancies, but a recent review on the subject concluded that no causative relationship has been proven.⁶⁰ Cases reported have ranged from GA preceding diagnosis of malignancy by 5 years, occurring concurrently, or developing as much as 27 years after the cancer. That said, there have been a number of case reports describing patients with GA and malignancy, including Hodgkin⁶¹⁻⁶³ and non-Hodgkin⁶⁴⁻⁶⁷ lymphoma, leukemia,^{68,69} and visceral malignancies, typically adenocarcinoma.^{70,71} A variety of GA subtypes were described in these patients, who were typically >60 years of age.⁷² Two association studies attempting to define whether a correlation exists between malignancy and GA concluded that there is no relationship.⁷² At this point, expert consensus remains that clinicians should consider screening for malignancy in older patients with GA, or those with atypical, widespread, or recalcitrant clinical presentations.^{60,66} Before a true association between GA and any of the conditions mentioned above can be determined, additional large-scale, controlled studies are necessary.

GA and its connection to HIV deserves special mention. The first discussion of GA in the setting of HIV/AIDS was probably in 1985, when it was noted that a number of noninfectious dermatoses including GA may have an increased incidence in patients with

AIDS.⁷³ A report of perforating GA in a patient with AIDS was described in 1987,⁷⁴ and several patients were subsequently reported to have “atypical” forms of GA—namely with disseminated papules or perforating GA.^{75,76} Four patients reported in 1989 were described as having a papular form of GGA, or an “extensive” LGA that appeared clinically similar to Kaposi sarcoma.⁷⁷ In 1999, Toro et al⁷⁸ published a study of 34 patients with GA and HIV. In these patients, 59% presented with AIDS, and unusual features of GA included oral lesions in 1 and perforating lesions in 2 patients. Moreover, GA was found to be generalized in 20 patients (59%) reported in this study, and in 15 of 23 (65%) of patients reported previously, suggesting that patients with HIV are more likely to have generalized disease than the general population. Clinically, the lesions were predominately papular rather than annular. Histopathologic findings included an interstitial pattern in 8 patients, palisaded in 18, perforating in 2, and mixed palisaded and interstitial in 6; no clinicopathologic correlation was discussed.⁷⁸ An editorial published at the same time drew attention to 2 HIV-infected individuals who presented with photodistributed GGA.⁷⁹ Six additional cases of HIV-associated GA were reported in 2000, with most patients presenting with papular lesions on extensor surfaces.⁸⁰ Some highly atypical cases of GA have also been reported in patients with HIV, including generalized umbilicated papules⁸¹ and a macular form with CD8⁺ T cells as the predominate infiltrate.⁸²

There are reports of antiretroviral drugs both improving⁸³⁻⁸⁵ and triggering⁸⁶ GA. Because AIDS is a problem with cell-mediated immunity, GA associated with HIV was initially interpreted as evidence against the hypothesis that GA is a delayed-type hypersensitivity reaction. However, given the complex interplay between HIV and the immune system, the story is probably not so straightforward. It is difficult to know whether the reported cases of GA are in fact true GA or rather are reactive granulomatous responses caused by HIV or antiretroviral drugs. Nonetheless, because many HIV patients in the general population are asymptomatic, the US Centers for Disease Control and Prevention currently recommends wider screening for HIV. As such, clinicians should assess patient risk factors and strongly consider HIV testing in patients with a new presentation of GA. Patients with perforating GA, or those with GGA with papules in particular should be screened, because these seem to be the predominant GA variants associated with HIV.

TRIGGERS

In addition to the reported associations between GA and the above systemic diseases, there have also been a number of reported triggers of GA. Some of the more unique triggers of the disease include a lightning strike, termed “lightning-strike granuloma,”⁸⁷ tattoo (caused by red pigment, developed after 37 years),⁸⁸ a bee sting,⁸⁹ and GA induced by an octopus bite.⁹⁰ GA has also been reported as a contact dermatitis⁹¹ and as an isomorphic response after saphenectomy.⁹²

There have been many other triggers reported to lead to the development of GA. In particular, GGA has been reported as developing after several vaccinations, including *Bacillus Calmette–Guérin*,^{93–96} hepatitis B,⁹⁷ tetanus and diphtheria toxoid,⁹⁸ and an antitetanus⁹⁹ vaccination. With that said, the inarguable health benefits of vaccinations far outweigh the exceedingly rare potential risk of GA development in all cases.

In a series of 5 patients, Kapoor et al¹⁰⁰ present a succinct review of the differences between an isotopic response (ie, developing a unique skin disease at the site of another healed and unrelated skin disease) and an isomorphic response (ie, the Koebner phenomenon). In these 5 patients, GA developed as an isotopic response at sites of previous herpes zoster infection. Multiple other case reports have demonstrated the same phenomenon,^{101–105} and GA has also been reported after varicella infection in 2 children.^{106,107} A case of GA after herpes zoster infection also showed features of an isomorphic response in an isolated report.¹⁰⁸

A number of medications have been implicated in triggering GA, though most are only in isolated case reports. These medications include TNF- α inhibitors, allopurinol,¹⁰⁹ topiramate,¹¹⁰ and gold therapy (for rheumatoid arthritis).¹¹¹ While some cases of GA associated with infectious hepatitis have improved after treatment with interferon, reports of interferon-alfa-induced GA have also been reported.¹¹² LGA has also been reported after injection of collagen for soft-tissue augmentation¹¹³ and after mesotherapy.¹¹⁴

TREATMENT

In 1982, Wilkin et al¹¹⁵ wrote “in general, successful treatment of any disease is probably inversely related to the number of recommended regimens.” It is not surprising that they were writing about GA, because there have been numerous reported treatment options for GA, many of which are supported by only small, uncontrolled case studies or series. In fact, in a series of 67 patients

with GA, there was no significant difference between duration of disease between treated and untreated patients.¹¹⁶ Further, it is estimated that around 50% of patients with LGA will spontaneously remit within 2 years, although recurrence is also common.^{117–120} While some initial reports suggested potassium iodide as an effective therapy for patients with GA,^{121,122} a 1994 double blind, placebo controlled trial¹²³ showed that the results were no better than placebo, prompting the authors to note “because of the potential for spontaneous waxing and waning of this disease, case reports and open studies that lack placebo control may give a false impression of efficacy of individual therapies.” This concept is important to keep in mind when interpreting the available data on treatment options for GA that are discussed below.

Despite the relative lack of evidence for effective therapies for GA, many patients desire treatment for symptomatic or cosmetic reasons, and it is important to discuss what options do exist. The intralesional injection of triamcinolone has strong expert consensus as a first-line therapy, but few studies have been designed to test this. In 1975, 52 patients with LGA were treated with intralesional injection of triamcinolone 5 mg/mL or sterile saline.¹¹⁷ Sixty-eight percent of those injected with steroid experienced complete clearance compared to 44% in the sterile saline group. Partial clearance was better in the saline group (33% vs 24%), and <50% of patients in both groups had recurrence of lesions after improvement. Because injection of medication leads to localized trauma of the skin, it is important to note that lesions of GA have also been shown to improve after trauma alone. Robinson, in 1953, described improvement after incision of lesions (he had previously noted improvement in lesions after biopsy).¹²⁴ Biopsy alone has also been reported to improve lesions of patch GA¹²⁵ and GGA.¹²⁶ Several reports of improvement after “scarification” (ie, the use of a 19-gauge needle drawn across the lesions until capillary bleeding occurs) have been described as successful.^{115,127} Improvement has also been described by “repetitive pricking”¹²⁸ and cryotherapy.¹²⁹

A number of studies have examined the role of phototherapy in treating GA. Psoralen plus ultraviolet A light phototherapy (PUVA) was first described as effective in patients with GGA in a report of 5 patients who improved within 1 month (after 2–3 treatments per week) of starting therapy.¹³⁰ In a follow-up report, an isolated patient with GGA was treated with bath PUVA and experienced improvement with this modality after 15 treatments.¹³¹ Bath PUVA was also reported to

improve an 11-year-old with GA.¹³² One report of PUVA for GGA without long-term treatment¹³³ prompted 3 additional reports of GGA that improved with PUVA but did require maintenance therapy to help prevent relapse.¹³⁴ In a retrospective study of 33 patients with GGA treated with PUVA (with the inclusion of 7 patients multiple times because they had experienced relapse in their disease and required additional therapy with PUVA), clearance was achieved in 50%, a partial response was seen in 41%, and only 9% showed no improvement. In long-term follow-up, 15 of 19 patients remained clear of disease at 6 months, 6 of 19 remained clear at 12 months, and 3 remained clear at 2 years.¹³⁵ Topical PUVA has also been described as therapy for LGA. In a study of 4 patients, all experienced improvement in the lesions after 4 weeks, with no recurrences after 4 months of follow-up.¹³⁶ UVA-1 therapy has also been described as effective in patients with GGA, although this modality is not widely available. In 1 report, 4 patients improved at least partially after 3 weeks of UVA-1, with 5 days per week of treatment.¹³⁷ A subsequent study of 20 patients with disseminated GA (ie, no clear description of the clinical findings) found that half experienced “excellent results” with 5 times weekly UVA-1 therapy.¹³⁸ Building on this, 4 patients were reported to have improvement in their “multiple localized GA” with higher doses of UVA-1.¹³⁹ In a study of 20 patients, 13 had their disease ameliorated after therapy with UVA-1.¹⁴⁰ While larger studies comparing different treatment modalities and placebo are needed, these findings do suggest that PUVA, or UVA-1 if available, should be considered for therapy of GA, particularly in patients with widespread disease.

Other forms of phototherapy have also been described as effective for patients with GA. Narrowband ultraviolet B light phototherapy was shown to improve disease in 1 patient after 24 total treatments.¹⁴¹ The excimer laser has also been described in reports of improving cases of GGA.¹⁴² It should be noted that while AEGCG may simply represent GA occurring on sun-damaged skin, there have been rare reports of GA occurring in a seasonal pattern, possibly correlated with increased exposure to ultraviolet light.¹⁴³ Similarly, a case of photo-induced GA has been reported after receiving paroxetine,¹⁴⁴ suggesting that the role of ultraviolet radiation in GA is incompletely understood.

A number of lasers have been used to treat patients with GA, and some early reported success was described with use of a pulsed-dye laser (PDL).^{145,146} However, in the largest study to date, 13 patients with GA (all women, with 5 localized cases

and 8 generalized cases) were treated with PDL and the results were disappointing. After 3 sessions, <33% of skin lesions treated showed improvement, and the treatment was associated with adverse effects, including postinflammatory hyperpigmentation. The authors did find that lesions of LGA improved more often than GGA (56% of LGA lesions treated showed improvement after 3 sessions compared to 14% for GGA). The authors did not compare treated lesions to untreated lesions.¹⁴⁷ Other lasers reported as successful in isolated case reports include an yttrium laser¹⁴⁸ and a neodymium-doped yttrium aluminium garnet laser.¹⁴⁹ Photodynamic phototherapy (PDT) has also been discussed as a therapy for patients with GGA and LGA, with some limited data suggesting a potential role for this therapy in refractory cases.¹⁵⁰⁻¹⁵²

Antimalarial drugs have been described for GGA since the first report of chloroquine 250 mg twice daily was reported as effective after just 2 months of therapy in 1959.¹⁵³ Hydroxychloroquine was first reported as effective in patients with GGA in 1987.¹⁵⁴ In a study of 6 children treated with antimalarials (4 with chloroquine and 2 with hydroxychloroquine), all achieved remission within 4 to 6 weeks of instituting treatment.¹⁵⁵ In a study of 9 patients treated for 4 months with hydroxychloroquine (9 mg/kg/d for 2 months followed by 6 mg/kg/day for 1 month, followed by 2 mg/kg/day for 1 month with half this dose used in the 1 child in the study), all achieved remission without relapse in the 9-month follow-up period.¹⁵⁶ One report of GGA in a photodistribution responded to therapy with chloroquine, with multiple recurrences when taken off the medication.¹⁵⁷ Hydroxychloroquine therapy is generally efficacious, and this therapy probably merits first-line consideration in patients with generalized disease—at least until additional studies are conducted to confirm or deny this conclusion.

TNF- α inhibitors have shown promise in treating widespread and recalcitrant granulomatous dermatitis, including GA. Case reports have described effectiveness in treating patients with GGA with a combination of adalimumab and methotrexate,¹⁵⁸ adalimumab alone,¹⁵⁹⁻¹⁶¹ and etanercept.¹⁶² GA with extensive involvement of the extremities has responded to infliximab^{163,164} and adalimumab.¹⁶⁵ A recent study reported 7 patients with generalized GA, all of whom initially responded to adalimumab, which was well tolerated in this cohort.¹⁶⁶ Similar to psoriasis and sarcoidosis where these drugs are used to treat the disease, TNF- α inhibitors have also been reported to trigger GA in a few instances.^{167,168} Additional studies are needed to show the risk/benefit profile of using TNF- α inhibitors to treat patients with GA and to justify their regular use.

Fumaric acid esters have received considerable attention in Europe for successfully treating noninfectious granulomatous processes generally, and GA specifically.¹⁶⁹⁻¹⁷⁴ Currently, fumaric acid esters are not widely used in the United States, with the first approval (for multiple sclerosis) occurring in 2013. Similarly, tranilast is a medication unavailable in the United States that has been described as effective in Japan for atopic dermatitis, and recently granulomatous diseases, such as sarcoidosis and GA. It is hypothesized that tranilast directly affects the monocyte–macrophage lineage cells, which could explain its effectiveness for these granulomatous conditions.¹⁷⁵

In 1954, vitamin E was first described as a treatment for GA (along with pantothenic acid derivatives), and 8 of 9 patients treated showed complete resolution.¹⁷⁶ In a retrospective cohort study of patients with “disseminated” GA (defined as having >10 lesions over at least 3 anatomic regions), the authors compared 21 patients treated with oral vitamin E to 17 patients treated with a “wait and see” approach. They found complete healing in 40% of patients, and improvement in an additional 30% of the patients treated with doses of vitamin E between 400 and 600 IU. However, lesions spontaneously disappeared in 31% and improved in 25% of untreated control patients.¹⁷⁷ Three patients with disseminated (apparently used in this article as equivalent to generalized) GA were treated with oral vitamin E and zileuton (a 5-lipoxygenase inhibitor). All 3 patients resolved after 2 to 3 months of therapy with minimal adverse effects.¹⁷⁸

In keeping with Wilkins et al’s premise¹¹⁵ that successful treatment is probably inversely related to the number of recommended regimens, there have been many additional treatments described as effective in small case reports or series. These include doxycycline,¹⁷⁹ rifampin, ofloxacin, and minocycline,^{180,181} dapsone,¹⁸²⁻¹⁸⁴ clofazimine,⁵⁹ allopurinol,¹⁸⁵ cyclosporine,¹⁸⁶⁻¹⁸⁸ methotrexate,¹⁸⁹ hydroxyurea,¹⁹⁰ alkylating agents, including chlorambucil,¹⁹¹⁻¹⁹⁴ niacinamide,^{195,196} defibrotide,¹⁷³ oral calcitriol,¹⁹⁷ topical imiquimod cream,¹⁹⁸⁻²⁰¹ topical pimecrolimus 1% cream,²⁰² topical tacrolimus 0.1% ointment,²⁰³⁻²⁰⁶ intralesional interferon-beta,²⁰⁷ intralesional interferon-gamma,²⁰⁸ isotretinoin, both alone²⁰⁹⁻²¹⁶ and in conjunction with topical pimecrolimus,²¹⁷ and etretinate.^{215,218} Efalizumab, a T cell modulator that is no longer available, has also been reported as effective for patients with recalcitrant GA.²¹⁹ Surgical excision is a reported option for lesions of subcutaneous GA, though recurrence is common.^{220,221} In the end, there are multiple options

for treating patients with GA, with limited evidence supporting any particular regimen. Clearly, however, more research is needed in this area.

In conclusion, there are 3 relatively common clinical variants of GA (ie, localized, generalized, and subcutaneous), and a number of rare subtypes. The histology is notable for mucin, with 2 patterns of granulomatous inflammation (ie, palisading and interstitial) typically seen. While the etiology is not known, GA may represent a reaction to a number of different stimuli leading to a common pathway, possibly mediated by delayed-type hypersensitivity and connective tissue damage. GA may be associated with HIV, diabetes, dyslipidemia, malignancy (especially hematologic), and thyroid disease, although stronger studies are needed to clarify these possible associations. Infections other than HIV and certain vaccines may also trigger GA, in addition to multiple other rarely reported stimuli. GA often self-resolves, but patients frequently seek treatment, and while data are lacking for many aspects of GA, treatment options in particular suffer from a paucity of large clinical trials. LGA may respond to intralesional glucocorticoid, and widespread disease is probably best initially treated with antimalarial drugs or phototherapy. GA is a common entity with a wide range of clinical presentations. It suffers from a lack of quality data, and additional studies are necessary to better elucidate the cause, triggers, associations, and treatment of this condition.

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Nevi and pregnancy



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Learning objectives

After completing this learning activity, participants should be able to distinguish physiologic versus worrisome changes in pigmented lesions of pregnant women; describe a biopsy protocol that is safe for pregnant patients; and list the methods for prevention and treatment of pigmentary changes during pregnancy, including melasma.

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Changes in the moles of pregnant women are frequently attributed to pregnancy, but recent studies suggest that pregnancy does not induce significant physiologic changes in nevi. It is common for nevi on the breasts and abdomen to grow with normal skin expansion, but studies that have examined melanocytic nevi on the backs or lower extremities have found no significant changes in size during pregnancy. Several studies have also investigated the belief that moles darken during pregnancy and have found insufficient evidence to support this idea. Dermoscopically, transient changes have been identified, but none are suggestive of melanoma. Results vary in terms of histologic changes seen in samples taken from pregnant women, but all authors agree that any histopathologic features consistent with melanoma should be viewed as melanoma and not attributed to pregnancy. Biopsy specimens should be obtained promptly from any changing mole that would raise concern for malignancy in a nonpregnant patient. Such procedures can be performed safely during pregnancy. (J Am Acad Dermatol 2016;75:661-6.)

Key words: biopsy; dermoscopy; histopathology; melanoma; mole; nevi; pregnancy.

INTRODUCTION

During pregnancy, increased levels of beta and alfa melanocyte-stimulating hormone, estrogen, progesterone, and beta-endorphin are thought to cause increased melanocyte stimulation and therefore hyperpigmentation.¹ The molecular pathways are not well understood, but the altered hormonal state of pregnancy may have distinct effects on melanocytic nevi.² Older literature has given rise to the popular belief that melanocytic nevi darken and

grow during pregnancy in response to hormonal changes.³⁻⁵ As such, changes in the moles of pregnant women are frequently attributed to pregnancy and are dismissed outright as benign.⁶ More recent studies, however, suggest that pregnancy itself does not induce significant changes in nevi. We review the relevant literature regarding melanocytic nevi during pregnancy and clarify best practice when presented with a changing mole in a pregnant patient.

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NEVI DURING PREGNANCY

Many reports have described changing nevi during pregnancy, but many of these are based on patients' own observations rather than objective criteria.⁷⁻¹⁰ In an early study by Sanchez et al,¹¹ 389 pregnant women were interviewed about their moles. More than 10% reported some type of change, including an increase in size and pigmentation, new onset of pruritus and pain, the development of new lesions, hair growth in existing lesions, or crust formation. Although the study did not measure the reported changes, biopsy specimens were obtained from 20 of these lesions and no cytologic atypia were found in any of the specimens. In another early study by Foucar et al,⁸ 33% of interviewed pregnant women reported changes in their moles. When examined, the majority of the lesions reported as changing were not melanocytic nevi but rather dermatofibromas and skin tags. One was actually found to be an attached tick. Biopsy specimens were obtained from 7 of the lesions, including those most concerning to the patients. These lesions were less likely to show atypia than lesions that patients did not report as having changed. These studies show the design fallacy of many of the historical studies examining this issue that have shaped the literature.

In recent years, several studies have sought to objectively determine what changes physiologically occur during pregnancy and what should be recognized as pathologic (Tables I and II). Patients with "dysplastic" nevus syndrome have been shown to have a significantly higher rate of nevi change during pregnancy, and are discussed under a separate heading.¹² For patients without dysplastic nevus syndrome or atypical mole syndrome, we have assessed those studies and grouped the findings across 4 categories: changes in size, changes in color, dermoscopic appearance, and histologic appearance.

Patients with dysplastic nevus syndrome

Key point

- Clinical and histologic changes in nevi during pregnancy may occur in patients with dysplastic nevus syndrome

Only 1 study has specifically reviewed the effects of pregnancy on the moles of patients with dysplastic nevus syndrome.¹² Seventeen women with dysplastic nevus syndrome were followed during 22 pregnancies and when they were not pregnant, serving as their own controls. Of the 17 women included, 76% were observed to have clinical changes in nevi, substantially higher than the patient-reported changes published by Sanchez

et al¹¹ and Foucar et al⁸ for women without dysplastic nevus syndrome. In addition, the rate of clinical change in these women was 3.9 times higher when they were pregnant than when they were not. When biopsy specimens were obtained from these lesions during pregnancy, they were twice as likely to show histologic dysplastic changes.

Changes in size

Key points

- Changes in the size of nevi most often occur on the front of the body, likely because of stretching of the skin during pregnancy
- Nevi on locations unaffected by skin stretching during pregnancy have not been shown to change significantly in size

When assessing nevi for changes in size, the most important factor to consider is location. In 1 study, 97 nevi measured from 56 pregnant women showed a statistically significant increased diameter from the first to the third trimesters.¹³ Of the 20 nevi that grew, 10 were located on the front of the body, 6 on the face and neck, 3 on the legs, and 1 on the back. The degree of enlargement was most significant for lesions on the front of the body. The authors concluded that the normal stretching and expansion of the skin of the breasts and abdomen might explain much of the growth seen in nevi during pregnancy. In support of this conclusion, another study examined changes in 56 nevi between the second and third trimesters and found that changes in size were most appreciable for lesions on the abdomen and breasts but not elsewhere.¹⁴ In the aforementioned study by Sanchez et al,¹¹ more lesions on the trunk were reported to have changed than in other locations.

To control for the effect of skin expansion during pregnancy, several studies have examined lesions exclusively in unaffected anatomic locations (Table I). One large study examined 129 lesions on the backs of pregnant white women.¹⁵ Of these, 8 were found to have changed in size—4 increased in diameter and 4 decreased in diameter. Overall, the mean change in size was 0 mm. The authors were unable to identify any risk factors for odds of changing given the small number of lesions. They did note that smaller nevi (2 mm in diameter) were more likely to expand, while larger nevi (>6 mm in diameter) were no more likely to increase than decrease in diameter. Other studies that have examined melanocytic nevi on the backs or lower extremities of pregnant women have also found no significant changes in size over the course of pregnancy.^{7,16,17}

Changes in color

Key point

- There is insufficient evidence to support the notion that moles darken during pregnancy

While changes in size are relatively simple to measure, objectively quantifying changes in color can be challenging. In 1 report, a patient experienced lightening of a giant congenital nevus and satellite nevi during 2 separate pregnancies. After each pregnancy, the patient had some, but not full, repigmentation.¹⁷ The authors documented this using photographs taken before, during, and after the pregnancies.

In a study using *in vivo* spectrophotometry to examine pigmentation,¹⁸ 381 melanocytic nevi on the backs and lower legs of 34 pregnant women were compared with 163 nevi on the backs and lower legs of 21 nulliparous women. Nevi were analyzed during the first trimester and in week 37 of pregnancy, and at a matched time interval for the nonpregnant subjects. In the pregnant group, 1 nevus was found to have increased slightly in epidermal pigmentation, and 14 (3.7%) showed a decrease; 18 nevi (4.7%) had an increase in dermal pigmentation while 4 (1.0%) had a decrease. In the nonpregnant control group, no nevi showed an increase in epidermal pigmentation, and 3 (1.8%) showed a decrease; 8 nevi (4.9%) had an increase in dermal pigmentation while none had a decrease. None of the changes, however, were statistically significant.

Dermoscopic appearance

Key points

- Transient dermoscopic changes can be identified in the melanocytic nevi of women, especially those located on the breast and abdomen
- Dermoscopic changes often reflect stretching of the skin and do not necessarily suggest melanoma

A number of studies have investigated changes in the dermoscopic features of melanocytic nevi during pregnancy (Table III). The first major study to do this examined 56 nevi on 12 pregnant patients in their second and third trimesters.¹⁴ Only nevi on the breasts and abdomen were observed to grow in size. Of those, lesions with a reticular pattern showed enlargement, where the pigment network simply became clearer and more widely meshed; lesions with a globular pattern showed an increased number of brown globules on the periphery. Neither pattern had any changes in shape. The authors explained these changes as part of the thinning and expanding that occurs in the skin in pregnancy, where deep

Table I. Summary of studies of changes in nevus size during pregnancy

Study	Findings during pregnancy	Locations
Akturk et al ¹³	Diameter increases	Changes most significant on abdomen and breasts
Strumia et al ¹⁴	Some changes in size	Only appreciable on abdomen and breasts
Pennoyer et al ¹⁵	No significant change in size	Back
Zampino et al ¹⁶	No significant change in size	Back
Grin et al ⁷	No significant change in size	Back

nests of nevi may be pushed closer to the surface, causing them to appear as junctional nests.

The following year, 21 nevi on the backs, faces, and necks of pregnant women were observed dermoscopically at ≤ 15 weeks' gestational age and again in the third trimester.¹⁹ At each visit, a total dermoscopy score was calculated for each lesion according to Stolz's *asymmetry, border, colors, and dermoscopic structures (ABCD)* rule,²⁰ where a higher score is indicative of greater suspicion for melanoma. Thickening of pigment network lines was observed in 2 nevi; brown globules and black dots increased in number, color, and size in 2 other nevi. The sample size was too small for statistical analysis, but the mean total dermoscopy score increased from 3.4 in the first trimester to 3.5 in the third trimester. Three of the 4 nevi that changed returned to their first trimester score by 6 months postpartum, and the fourth patient was lost to follow-up.

A comparative dermoscopic examination of moles on the backs of pregnant women in the first and third trimesters, and again 6 months after delivery,¹⁶ found that the number of vessels increased between the first and third trimesters but normalized after delivery. The authors opined that the dermoscopic changes paralleled typical vascular changes seen elsewhere on the skin during pregnancy and were caused by increased blood volume and vessel proliferation. The total dermoscopy score, again calculated according to Stolz's ABCD rule,²⁰ increased between the first and third trimesters and then decreased significantly after delivery. There was also a decrease in overall pigmentation and prominence of pigment network after the first trimester, likely because of less sun exposure at the later appointments—subjects were not allowed sun exposure in the 4 weeks before the second 2 visits.

Table II. Summary of studies of histologic changes in nevi during pregnancy

Study	Histologic changes
Foucar et al ⁸	No significant difference in overall atypia, though slightly more atypical than nonpregnant female controls and similar to male controls Pregnant women more atypical than controls, specifically in mitotic activity, lentiginous proliferation, other cytologic atypia, demarcation of melanocytes at lateral margins of lesion, and the presence of small nevus cells in lower dermis
Sanchez et al ¹¹	No significant differences between pregnant women and age-matched female controls
Chan et al ²²	Clustered melanocytes with specific appearance in 83% of nevi from pregnant patients Multinucleated melanocytes seen exclusively in controls Significantly higher mitotic rate and number of mitotic figures compared with age-matched controls, and marginally higher Ki-67 proliferation index

Another dermoscopic analysis was performed on 82 nevi of pregnant women from locations all over the body in the first and third trimesters.¹³ Pattern analysis of these lesions revealed no significant differences between visits, but there was new dot development in 6 of the nevi, 4 of which were located on the front of the body. There was also a statistically significant increase in the total dermoscopy score between the first and third trimesters. In a study using digital dermoscopy to evaluate 206 nevi in pregnant patients, excluding those on the breasts, abdomen, and acral regions,²¹ lesions were observed between weeks 5 and 8, weeks 39 and 41, and again 1 year after delivery. Multivariate analysis of variance revealed that during pregnancy the pigment network thickens, becoming more prominent, and globules of nevi with a globular pattern darken. Both of these changes regressed within 1 year after delivery. It was also found that during pregnancy the reticular pattern of nevi becomes less organized, and the size and distribution of globules becomes less homogenous. These changes persisted 12 months after delivery.

In summary, transient changes in dermoscopy have been identified in the melanocytic nevi of women, especially those located on the breast and abdomen. However, none of these changes were suggestive of melanoma.

Histologic appearance

Key points

- Some authors have described histologic differences in biopsy specimens obtained from nevi in pregnant women
- Any histopathologic features consistent with melanoma should be viewed as melanoma and not attributed to pregnancy

To assess differences in histologic features, several studies have compared specimens from pregnant women to nonpregnant controls (Table II). One

group compared 128 nevi from pregnant women to 51 nevi from nonpregnant women and 50 nevi from men.⁸ For each specimen, 9 histologic factors were graded by 2 of the authors, and an overall atypia score was determined. Although not statistically significant, the nevi from pregnant women had slightly higher atypia scores than those from nonpregnant female controls. Atypia scores from the pregnant women and male controls were similar. When looking at the 9 histologic variables separately, pregnant women had the highest mean scores for mitotic activity, lentiginous proliferation, other cytologic atypia, demarcation of melanocytes at lateral margins of lesion, and presence of small nevus cells in lower dermis. In this study, it is important to note that clinically atypical nevi were searched for in patients in the pregnant group, whereas clinically atypical nevi were excluded in the nonpregnant and male groups. When no clinically atypical nevi were present, the pregnant patient volunteered a nevus of her choice. The authors stated that this bias was intentionally introduced to produce a control group whose nevi were similar clinically to the nevi in the pregnant population. In addition, pregnant women had their nevi excised in the summer, while control lesions were sampled during all seasons. Even with these potential limitations, the findings of the study were not statistically significant.

In the study by Sanchez et al,¹¹ biopsy specimens were obtained from 26 of the lesions that were self-reported to have changed and compared to nevi of age-matched female controls. Specimens were examined for specific histologic features, including melanocytic hyperplasia, elongation of rete ridges, papillary fibroplasia, inflammatory cell infiltrates, depth of cellular maturation, vascular dilation, symmetry, circumscription, and cellular atypia. No cytologic atypia was found in any of the specimens, no significant differences were found between the 2 groups, and no relationship was seen between clinical and histologic changes.

Table III. Summary of studies of dermoscopic changes in nevi during pregnancy

Study	Locations assessed	Stages compared	Changes noted during pregnancy	Postpartum status
Strumia et al ¹⁴	All	Second and third trimesters	Pigment network became clearer and more widely meshed with growth Increased number of brown globules on the periphery with growth	Not assessed Not assessed
Gunduz et al ¹⁹	Back, face, and neck	First and third trimesters	Thickening of pigment network lines in 2 of 21 nevi Brown globules and black dots increased in number, color, and size in 2 of 21 nevi Increased TDS	Not assessed Not assessed Returned to first trimester score by 6 months*
Zampino et al ¹⁶	Back	First and third trimesters	Increased number of vessels Decrease in pigmentation and prominence of pigment network Increased TDS	Normalized within 6 months after delivery Progressive through 6 months after delivery Decreased within 6 months after delivery
Akturk et al ¹³	All	First and third trimesters	New dot development in 6 of 82 nevi Increased TDS	Not assessed
Rubegni et al ²¹	Excluded breasts, abdomen, and acral	First and third trimesters	Increase in prominence and thickening of pigment network Darkening of globules in nevi with a globular pattern Decreased organization of reticular pattern Less homogeneity in size and distribution of globules	Regressed within 12 months after delivery Regressed within 12 months after delivery Persisted 12 months after delivery Persisted 12 months after delivery

TDS, Total dermoscopy score.

*3/4 returned, 1 lost to follow-up

In another paper examining histologic features, 16 nevi from pregnant women were compared to 15 nevi from location- and age-matched controls.²² The authors found that 83% of nevi excised from pregnant patients exhibited clusters of melanocytes with a specific appearance, which they termed, “superficial micronodules of pregnancy.” This appearance was described as “rounded clusters of 3 to 20 large epithelioid melanocytes with prominent nucleoli, abundant pale eosinophilic cytoplasm, and occasional fine melanosomes.” The authors speculated that this might represent a histopathologic characteristic of nevi from pregnant women; however, a quarter of the control cases also had this feature. Interestingly, multinucleated melanocytes, thought to represent a feature of senescence seen in common nevi, were seen only in the control nevi. In addition, there was a significantly higher mitotic rate and number of

mitotic figures observed in nevi from the pregnant group. There was also a marginally higher Ki-67 proliferation index in nevi from pregnant patients compared with control nevi. The authors inferred that there may be both increased melanocyte proliferation and cell cycle progression during pregnancy.

The results of these studies vary in terms of the trends seen and their significance, but all authors concluded that the degree of atypia seen in all cases would not have raised concern for melanoma, even if taken from nonpregnant patients. As such, any histopathologic features consistent with melanoma should be viewed as melanoma and not attributed to pregnancy.

Biopsy specimens during pregnancy

Key points

- Lidocaine is classified by the US Food and Drug Administration as pregnancy category

B, and can be safely used for local anesthesia during pregnancy

- **There is no need to delay obtaining a biopsy specimen from a suspicious melanocytic lesion during pregnancy**

The most commonly used local anesthetic during routine dermatologic biopsy procedures and excisions is lidocaine. While it does cross the placenta,²³ lidocaine has been classified by the US Food and Drug Administration (FDA) as category B, and can be used safely during pregnancy. Epinephrine has been classified by the FDA as category C, and its use to augment hemostasis and prolong the effects of lidocaine is more controversial. While no adverse events have been documented in humans, studies in sheep and in vitro studies with human uterine arteries have shown that epinephrine at high doses can cause spasm and reduce flow through the uterine artery.²³⁻²⁵ For this reason, many advise to use lidocaine without epinephrine in pregnant patients.²⁶

Lidocaine with epinephrine is actually classified as FDA category B, and while there are no studies supporting this, the likelihood of significant effect on the fetus is low. Serum levels of endogenous epinephrine during a stressful event exceed serum levels caused by injections of lidocaine with epinephrine.²⁴ The addition of epinephrine to lidocaine for obtaining a biopsy specimen in a pregnant patient may actually provide an advantage²⁷ in that its vasoconstrictive effects can reduce peak serum levels of lidocaine in the mother, and therefore decrease placental transfer of lidocaine to the fetus.²⁴

In conclusion, based on the available evidence, changes that occur in a nevus of a pregnant patient should not be disregarded as a physiologic consequence of pregnancy. Any change that would raise concern for malignancy in a nonpregnant patient should do so in a pregnant patient. While many dermatologists prefer to delay procedures until after pregnancy, obtaining a biopsy specimen from a changing mole in a pregnant woman should be done promptly so as not to delay the diagnosis of a melanoma.

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Pregnancy and melanoma

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Learning objectives

After completing this learning activity, participants should be able to identify risk factors for melanoma during or after pregnancy; determine prognosis if diagnosed with melanoma before, during, or after pregnancy; and discuss the evidence base concerning an approach to managing patients with melanoma during pregnancy.

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Malignant melanoma is the most common malignancy during pregnancy, and is diagnosed during childbearing age in approximately one-third of women diagnosed with melanoma. The impact of hormonal changes during pregnancy and from iatrogenic hormones on melanoma is controversial. Women undergo immunologic changes during pregnancy that may decrease tumor surveillance. In addition, hormone receptors are found on some melanomas. In spite of these observations, the preponderance of evidence does not support a poorer prognosis for pregnancy-associated melanomas. There is also a lack of evidence that oral contraceptives or hormone replacement therapy worsens melanoma prognosis. (J Am Acad Dermatol 2016;75:669-78.)

Key words: hormone replacement therapy; melanoma; oral contraceptives; pregnancy; prognosis; review.

INTRODUCTION

According to a recent population-based Swedish cancer registry study,¹ malignant melanoma (MM) is the most common malignancy reported during pregnancy. In addition, MM is one of the most common malignancies to affect young women,² and approximately one-third of all women diagnosed are of childbearing age.³

Controversy concerning the impact of pregnancy on MM began in the 1950s, with case reports suggesting that pregnancy may induce nevus

transformation into MM or increase the risk of metastasis for existing MMs.^{4,5} Pregnancy is considered to induce a state of immunosuppression, perhaps allowing for tumor progression.⁶ The argument that MM is a hormonally responsive tumor⁷ has been fueled over the years by reports showing changes in pigmentation during pregnancy, increased MM incidence after puberty, and the presence of progesterone and estrogen receptors in some MMs.^{8,9} These factors seemingly culminate in a set of circumstances that appear to favor a poorer

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prognosis for those diagnosed with MM during pregnancy or in the immediate postpartum period. Since our first review of this topic in the *Journal* 22 years ago,¹⁰ more data have become available for analysis. Nonetheless, the impact of pregnancy on MM has not yet been resolved and continues to be an area of debate.¹¹

This review addresses multiple controversies regarding MM in women of childbearing age: (1) immunologic changes during pregnancy and their impact on tumor surveillance; (2) prognostic consequences for women diagnosed with MM during pregnancy, in the postpartum period, or before pregnancy; (3) the influence of hormonal changes during pregnancy and iatrogenic hormones (eg, oral contraceptive pills or hormonal replacement therapy) on MM; (4) characteristics of MMs associated with pregnancy; and (5) counseling of women diagnosed with MM regarding future pregnancies and the use of iatrogenic hormones.

IMMUNOLOGIC CHANGES DURING PREGNANCY

Key points

- There are similarities between the physiologic state of pregnancy and the immunosuppressed state that may foster the growth and tolerance of cancer cells
- There is no specific evidence suggesting that the immunosuppressed state may lead to melanoma development or progression

The immune system of the pregnant woman must protect both mother and fetus from pathogens, while tolerating the fetus, which contains foreign paternal antigens.¹² Decades of research have elucidated the complexity of the maternal–fetal interface; cytotoxic adaptive immune responses are significantly diminished, innate immunity remains intact, and regulatory adaptive immunity is enhanced.

The expansion of CD4⁺ CD25⁺ regulatory T cells (Tregs) are essential for allowing the fetus to survive.¹³ Tregs mediate tolerance in pregnancy as well as cancer.⁶ These cells are increased in cancer and may be implicated in impaired antitumor immunity, suppression of effector T lymphocyte proliferation, and increased tumor vascularity.⁶

Uterine natural killer cells (uNKs), found in the decidua of the pregnant uterus, are the most common immune cells found at the maternal–fetal interface. uNKs are more immunomodulatory than cytotoxic and may play a role in inducing tolerogenicity and angiogenesis in the decidua and placenta. Certain malignancies have shown a similar reduction in NK cell cytotoxic activity.⁶

In addition, the maternal–fetal interface's transition from the inflammatory T helper cell 1 (T_H1)–predominant environment to the immunologically tolerant T helper cell 2 (T_H2) milieu in the first 2 trimesters parallels immunologic alterations seen in malignancies.^{14,15} The T_H2-driven environment favors tumor survival, and T_H2 cytokines are elevated in patients with metastatic compared to resected MMs.¹⁵

While there is no compelling body of evidence to suggest that pregnancy induces specific immunologic changes that lead to the development or spread of MM, some investigators have observed similarities between the physiologic state of pregnancy and the immunosuppressed state that fosters the growth and tolerance of cancer cells.⁶

Prognosis for the woman diagnosed with MM during pregnancy, in the postpartum period, and before pregnancy

In the present review, we considered only studies that included Breslow depth, appropriate control groups, and stage of disease. Many of the early case series predicting prognosis for those diagnosed with MM during pregnancy or in the postpartum period did not account for MM tumor depth and were not controlled. Since the 1980s, there have been a number of small, controlled studies and large, population-based cohort studies that uniformly suggested no influence of pregnancy on the prognosis of MM. Some of the recent large cohort studies do not separate MM diagnosed during pregnancy from MM diagnosed during the postpartum period (varies by study). Investigators refer to these cases as pregnancy-associated MM (PAMM). The definition of PAMM varies across studies, with the window of diagnosis varying from diagnosis during pregnancy to diagnosis as far out as 5 years postpartum.¹⁶ Fortunately, some of these studies perform additional analyses in which the group diagnosed during pregnancy was separated from those diagnosed in the postpartum period. While the population-based cohort studies offer the advantage of large numbers of patients, data are often incomplete concerning Breslow depth of the primary tumor and stage of disease. Some studies do not report the duration of follow-up or adjust for possible confounding factors. Overall, there are a limited number of consistent and well-controlled studies concerning the influence of pregnancy on the prognosis of melanoma. Nonetheless, we have based our conclusions on the best data available.

MELANOMA DIAGNOSED DURING PREGNANCY

Key point

- While controversial, women diagnosed with malignant melanoma during pregnancy do not appear to have a poorer prognosis than nonpregnant controls

Overall, most small, controlled studies¹⁷⁻²³ and large, population-based cohort studies^{16,24-27} have reported no significant influence of pregnancy on survival in women diagnosed with MM compared with women not pregnant at the time of diagnosis (Table I). Two studies^{17,18} from 1 institutional database showed a shorter disease-free interval (DFI) in the pregnant group compared to controls, but 3 other trials^{19,21,22} that calculated DFI did not find any effect (Table I). While we have previously discussed the small studies in detail,²⁸ descriptions of the large cohort studies are provided herein.

In a retrospective cohort using data from the Swedish National and Regional Registries, Lens et al²⁴ compared 185 women diagnosed with MM during pregnancy to 5348 women of similar age who were not pregnant at the time of diagnosis. There was no statistically significant difference in overall survival between groups (χ^2 1 [r]=0.84, $P = .361$). The influence of pregnancy status at the time of MM diagnosis was assessed by multivariable Cox regression model for 2101 women for whom data was available concerning Breslow depth of primary MM, Clark level, anatomic site of MM, and age; pregnancy status at time of MM diagnosis was not related to death (hazard ratio [HR], 1.08 [95% confidence interval {CI}, 0.60-1.93]).²⁴ Five years later, these investigators calculated risk of cause-specific survival from their database, and found no significant difference when comparing women diagnosed with MM during pregnancy compared to controls using the log rank test ($\chi^2=0.11$; $P = .738$) or with multivariable analysis (HR, 1.17 [95% CI, 0.59-2.32]; $P = .658$).²⁵

O'Meara et al²⁶ used a database that linked California hospital discharge records with the California Cancer Registry to compare 412 women diagnosed with MM during pregnancy and ≤ 1 year postpartum with 2451 age-matched nonpregnant women diagnosed with MM. Kaplan-Meier survival curves showed no significant difference between these groups (log-rank test; $P = .13$). A Cox proportional hazards model was used to assess the impact of various factors to death, including pregnancy status, Breslow depth of primary MM,

stage of disease, and age. When the analysis included only the 145 women diagnosed during pregnancy (plus 4 women diagnosed at delivery), pregnancy status was not related to death (HR, 0.79; $P = .570$). In addition, a mortality rate was reported as 8.3% of the 145 women diagnosed with MM during pregnancy, compared to 9.8% in the control group (no statistical analysis performed).

Using data from the Cancer Registry and the Medical Birth Registry of Norway, Stensheim et al²⁷ reported an increased risk of MM-related death in 160 pregnant patients compared with 4460 nonpregnant patients (HR, 1.52 [95% CI, 1.01-2.31]). However, once the melanomas were adjusted for anatomic location, there was no statistically significant difference in survival (HR, 1.45 [95% CI, 0.96-2.21]).

A population-based retrospective cohort study based on data from the Swedish Cancer and Multi-Generation Registers compared cause-specific mortality in 1019 women with MM diagnosed during pregnancy or ≤ 2 years postpartum with 5838 women not pregnant or within 2 years postpartum at time of diagnosis.¹⁶ When the PAMM group was limited to the 247 women with MM diagnosed during pregnancy and compared to controls, there was no significant difference in mortality (HR, 0.79 [95% CI, 0.44-1.41]), with the HR adjusted for time since diagnosis, age at diagnosis, calendar year at diagnosis, education, parity, and tumor location.

A recent meta-analysis reported increased risk for MM-related death (pooled HR, 1.56 [95% CI, 1.23-1.99]).¹¹ However, the methodology of this study has come under scrutiny by several investigators,²⁹ including our group.³⁰ In our own meta-analysis of studies evaluating prognosis for PAMM, we found a nonsignificantly elevated risk of death for pregnant patients diagnosed with melanoma (HR, 1.19 [95% CI, 0.96-1.48]).³⁰

A single institutional retrospective study recently reported a mortality rate of 20% and a 5.10 greater odds of death ($P = .03$) in patients with PAMM than in nonpregnant women. The mortality rate and odds ratio reported are substantially higher than all previous studies in the literature. This study is difficult to interpret because it inconsistently reported staging, included only a small number of PAMM cases, and did not use proper survival analysis techniques.²³

There are multiple limitations of these studies. The small studies were frequently limited to early-stage disease (American Joint Committee on Cancer stage I or II), while the large, population-based cohort studies included all stages of disease,

Table I. Summary of controlled studies on melanoma diagnosed during pregnancy

Study	No. of pregnant patients	No. of controls	Duration of follow-up	Did pregnancy influence survival?	Did pregnancy result in a shorter DFI?	Stage of disease
Reintgen et al ¹⁷	58	585 not pregnant at time of dx or within 5 y	5 y	No	Yes ($P = .04$)	I
Slingluff et al ¹⁸	88 (continuation of patient base used by Reintgen et al ¹⁷)	79 not pregnant at time of dx	6 y	No	Yes	I
McManamny et al ¹⁹	23	243 not pregnant at the time of dx or afterwards	2 months to 20 y	No	No	I
Wong et al ²⁰	66	619 not pregnant at time of dx; 66 matched for Breslow depth, anatomic location of primary, lesion, and histopathologic subtype	N/A	No	Actuarial DFI curves not calculated; no mean DFI was longer for pregnant patients (37.7 months) vs controls (27.3 months)—statistical analysis not done	I
MacKie et al ²¹	92 (group 2)	143 not pregnant at time of dx (group 3); 68 patients subsequently became pregnant (group 4); 85 patients who were pregnant before dx (group 1)	N/A	No (when groups 1-4 compared)	No	I
Daryanani et al ²²	46	368 not pregnant at time of dx and matched for age and sex	109 months (median)	No (10-year survival curve)	No	I and II
Lens et al ²⁴	185	5348 not pregnant at time of dx	11.6 y (median)	No	N/A	All
O'Meara et al ²⁶	145	2451 not pregnant at time of dx	N/A	No; HR, 0.79 ($P = .570$)	N/A	All
Stensheim et al ²⁷	160	4460 not pregnant at time of dx or after dx	11.9 y (median)	No; HR, 1.45 (95% CI, 0.96-2.21)	N/A	All
Johansson et al ¹⁶	247	5838 not pregnant at time of dx or >2 y postpartum at dx	Up to 10 y	No; HR, 0.79 (95% CI, 0.44-1.41)	N/A	All
Tellez et al ²³	19	421 not pregnant within 1 year of dx	91 months	Yes (analysis included 1-year postpartum); OR = 5.10 ($P = .03$)	N/A	All (including 35% in situ)

CI, Confidence interval; DFI, disease-free interval; dx, diagnosis; HR, hazard ratio; N/A, not available; OR, odds ratio; y, year.

and information concerning stage varied widely. In the study by Stensheim et al,²⁷ localized MM was seen in 89% of pregnant patients. O'Meara et al²⁶ reported stage of disease for 108 of 145 (74.5%) pregnant patients, and 92.6% had localized MM. Johansson et al's study was missing stage in 39.4% of cases.¹⁶ Stage of disease was not reported in the Swedish study by Lens et al.²⁴

In summary, based on a small number of appropriately controlled studies, women diagnosed with MM during pregnancy do not appear to have a poorer prognosis than nonpregnant controls.

MELANOMA DIAGNOSED IN THE POSTPARTUM PERIOD

Key point

- Overall, multiple large studies have found that the postpartum period does not significantly influence prognosis for women diagnosed with melanoma for ≤ 5 years postpartum

While there are few studies reporting the prognosis for MM diagnosed after pregnancy, there appears to be no significant influence of diagnosis ≤ 5 years postpartum on MM prognosis (summarized in Table II). In the most recent and largest study from the Swedish Cancer and Multi-Generation Registers¹⁶ there was no evidence for worse prognosis for PAMM (MM during pregnancy and up to two years postpartum), except for a difference in the second year postpartum that was not statistically significant. Analysis was extended through five years postpartum and no differences in survival by year were found.¹⁶ In an English cancer registry study also examining breast cancer and Hodgkin's lymphoma, Moller et al.³¹ reported significantly increased mortality in the first year postpartum (HR 2.06, 95% CI 1.42-3.01) compared with women in the control group, but not for MM diagnosed in the second through fifth year postpartum. Andersson et al¹ found fewer than expected melanomas diagnosed during pregnancy and a higher rate diagnosed 6 months postpartum. This observation may represent a rebound effect, caused by a delay in diagnosis, and could account for the increased mortality seen by Moller et al³¹ in their first year postpartum group.

In summary, 5 controlled studies have examined the impact on prognosis when MM is diagnosed after pregnancy, ≤ 5 years postpartum. One study³¹ showed a negative influence in the first year after delivery, but overall, the evidence to date does not suggest a worse prognosis for the woman diagnosed with MM ≤ 5 years postpartum.

MELANOMA DIAGNOSED PRIOR TO PREGNANCY

Key point

- There is no influence on survival when melanoma is diagnosed before pregnancy

Several studies have found no significant impact on prognosis when MM is diagnosed before pregnancy. In the retrospective population-based cohort study by Lens et al,²⁴ a secondary analysis was performed comparing 966 women with MM diagnosed before pregnancy to 4567 women without pregnancy after the MM. In a multivariable Cox regression model, MM diagnosed before pregnancy was not related to survival after adjustment for Breslow depth of tumor, tumor site, Clark level, and age (HR, 0.58 [95% CI, 0.32-1.05]). Reintgen et al¹⁷ found no difference in survival between 43 women who became pregnant within 5 years of their MM diagnosis and 337 nonpregnant age-matched controls in both univariate and multivariable models. Similarly, MacKie et al²¹ compared 85 women who became pregnant after their diagnosis of MM to 143 who completed all of their pregnancies before their MM and found no significant difference in overall survival or DFI. In summary, there appears to be no influence on survival when MM is diagnosed before pregnancy.

CHARACTERISTICS OF PREGNANCY-ASSOCIATED MELANOMAS

Key point

- Most studies suggest that women diagnosed with melanoma during pregnancy do not have thicker primary tumors, tumors located in poorer prognostic anatomic sites, or other characteristics that would favor a negative impact on survival

Other issues variably addressed in studies of PAMM have included the influence of pregnancy on Breslow depth, anatomic location, and other prognostic measures. Of the 10 studies that have reported Breslow depth of primary tumors in pregnant women,^{17-22,24,26,27,32} only two^{21,32} have reported thicker Breslow depths compared to nonpregnant controls. One large, population-based cohort study observed no significant difference in tumor depth overall in pregnant patients compared with nonpregnant controls, except for MMs diagnosed in the third trimester.²⁴ With regard to primary MM location, only 2 of the large, population-based cohort studies have observed an increased frequency of MMs in poor prognostic sites.

Table II. Summary of controlled studies on melanoma diagnosed after pregnancy

Study	No. of patients in study group	No. of controls	Duration of follow-up	Did pregnancy have a statistically significant effect on survival? HR (95% CI) or other	Stage of disease at diagnosis
Tellez et al ²³	22 diagnosed within 1 year postpartum	421 not pregnant within 1 year of dx	91 months	Yes (analysis included dx during pregnancy); OR = 5.10 ($P = .03$)	All (including 35% in situ)
Johansson et al ¹⁶	422 diagnosed within 1 y postpartum	5838 not pregnant or >2 y postpartum at dx	Up to 10 y	No, 0.97 (0.64-1.45)	All stages, 84.6% of staging data N/A
	350 diagnosed within 2 y postpartum	5838 not pregnant or >5 y postpartum at dx		No, 1.42 (0.98-2.06)	
	275 diagnosed within 3 y postpartum	4998, not pregnant or >5 y postpartum at dx		No, 1.17 (0.74-1.86)	
	296 diagnosed within 4 y postpartum	4998, not pregnant or >5 y postpartum at dx		No, 0.87 (0.54-1.40)	
	269 diagnosed within 5 y postpartum	4998, not pregnant or >5 y postpartum at dx		No, 1.08 (0.69-1.69)	
Moller et al ³¹	306 diagnosed within 1 y postpartum	16,222 not within 1 y postpartum	Up to 11 y	Yes, 2.06 (1.42-3.01)	All stages; 28% of staging data N/A
	267 diagnosed within 2 y postpartum	14,962 not within 2 y postpartum at dx		No, 1.22 (0.73-2.05)	
	225 diagnosed within 3 y postpartum	13,698 not within 3 y postpartum at dx		No, 1.14 (0.62-2.08)	
	229 diagnosed within 4 y postpartum	12,229 not within 4 y postpartum at dx		No, 1.33 (0.76-2.32)	
	201 diagnosed within 5 y postpartum	10,668 not within 5 y postpartum at dx		No, 1.18 (0.61-2.30)	
Stensheim et al ²⁶	126 diagnosed within 6 months postpartum	4460 nonpregnant or >6 months postpartum	13.8 y (median)	No, 1.10 (0.65-1.85)	All; "extent of disease unknown" for 7% of controls and 5% of study group
Mackie et al ²¹	143 diagnosed after completing all pregnancies (group 3)	92 diagnosed during pregnancy (group 2) 68 with dx between pregnancies (group 4) 85 pregnant before diagnosis (group 1)	N/A	No significant difference in survival or DFI	Stage I
O'Meara et al ²⁵ (population-based cohort)	263	2451 nonpregnant	109 months (median)	No, 0.58 ($P = .162$)	All; 26% of staging data N/A for study group

CI, Confidence interval; DFI, disease-free interval; dx, diagnosis; HR, hazard ratio; N/A, not available; OR, odds ratio; y, year.

Stensheim et al²⁷ reported 54% of pregnant patients having MMs on axial locations, compared with 41% of the nonpregnant controls, in whom legs were the most common site. This difference was statistically significant, though data from this analysis were not shown. Johansson et al¹⁶ reported that women diagnosed during pregnancy were more likely than nonpregnant controls to have MMs on the trunk, although this finding was not statistically significant ($P = .082$).

A recent retrospective review³³ focused on the clinicopathologic characteristics of 34 MMs diagnosed during pregnancy or within 1 year postpartum and compared those with MMs in age- and disease stage-matched women who were not pregnant at the time of diagnosis or within 1 year postpartum. These investigators observed no significant difference between the groups for Breslow depth, ulceration, mitotic rate, stage of disease, anatomic location of MM, histologic subtype, Clark level, regression, necrosis, or vascular invasion. The only difference noted was more marked inflammation around the tumor in the PAMM group; however, the level of inflammation described in all cases was "mild."

In summary, the majority of data for analysis suggest that women diagnosed with MM during pregnancy do not have thicker primary tumors, tumors located in poorer prognostic anatomic sites, or other characteristics that would favor a negative impact on survival.

INFLUENCE OF HORMONES ON MELANOMA

Key points

- There is an association between estrogen receptor-beta expression and melanocytic lesions, with a suggestion that melanoma is a hormone-sensitive malignancy
- The clinical relevance of estrogen in melanoma and pregnancy-associated melanoma remains unclear

Several observations have prompted investigation into the potential influence of hormones on patients with MM. It has been noted that women have a survival advantage over men diagnosed with MM and that hormone receptors are detected in MMs. We examine what is known about the clinical relationship between hormonal therapies, such as oral contraceptive pills (OCPs) and hormonal replacement therapy (HRT), and MM. We subsequently review the laboratory evidence for hormonal influences on MM.

The majority of data on OCPs and MM are based upon epidemiologic studies evaluating the risk of developing MM associated with use of OCPs. In our recent review,³⁴ we reported that at least 22 studies have examined the relationship between OCP use and MM development; the majority of these studies show no effect of "ever use" of OCPs compared with those who never used OCPs. Two of the earliest studies^{35,36} suggested an enhanced risk of MM in OCP users but did not account for potential confounders, including sun exposure history. Other studies showing an increased risk of MM associated with a long duration of OCP use generally did not control for potential confounders, included small numbers of MM cases, and sometimes lacked statistical significance of their results.³³ A large cohort study using the Nurses' Health Study (NHS) and NHS II cohorts reported enhanced risk of MM in current users versus never users of OCPs (relative risk = 2.0 [95% CI, 1.2-3.4]).³⁷ This study reported a small number (n = 23) of cases of MM in current OCP users and lacked information on sun exposure.

Two meta-analyses and a pooled analysis of 10 case control studies reported no impact of OCPs on the risk for MM. A meta-analysis of 18 studies³⁸ reported a summation OR of 0.95 (95% CI, 0.82-1.15). A pooled analysis³⁹ of 10 case control studies, which included 3796 cases of melanoma in the setting of ever OCP use and 9442 controls with never OCP use, reported no increase in risk of MM (pooled OR = 0.86 [95% CI, 0.74-1.01]). They found no relation with length of use, age at first use, or current use. In addition, there was no elevated risk seen in past users, even those with long past durations of use.³⁸ These data provide strong evidence against OCP use as a risk factor for the development of MM.

There are a limited number of studies analyzing the relationship between HRT and MM. Gupta et al³⁴ identified 12 such studies, 10 of which showed no association between the use of HRT and MM risk. The 2 studies that reported increased risk did not control for potential confounding variables.³⁴ In addition, 1 of these studies did not show a trend for increased MM risk associated with longer duration of HRT use, as one would expect if a true relationship existed.³⁴ A randomized trial from the Women's Health Initiative examined the incidence of MM in 27,347 postmenopausal women who were randomized to receive either: (1) conjugated equine estrogen plus medroxyprogesterone or placebo (if intact uterus) or (2) estrogen alone or placebo (if had hysterectomy). Rates of incident MM were similar between the active hormone group

(estrogen plus medroxyprogesterone or estrogen alone) and placebo groups after 6 years of follow-up.⁴⁰

Questions concerning the role of hormones in MM have prompted laboratory studies examining estrogen receptors in melanoma. Estrogen receptor alpha (ER-alpha) has never been shown in benign nevi, dysplastic nevi, primary MM, metastatic MM, or pregnancy-associated MM.²⁸ In contrast, ER-beta receptor may be expressed in dysplastic nevi or MM. ER-beta may play a role in other malignancies, including breast, colon, ovary, and prostate cancers. ER-beta receptor expression was seen in all 94 pigmented lesions in 1 immunohistochemical (IHC) study, including banal nevi, dysplastic nevi with varying degrees of cytologic atypia, lentigo malignas, and MMs.⁴¹ Inexplicably, staining was most intense for ER-beta in dysplastic nevi with severe atypia and lentigo malignas. In addition, a strong correlation was observed between ER-beta expression and the proximity of MM cells to keratinocytes.⁴¹ Among 36 invasive MMs, loss of ER-beta expression correlated substantially with increased Breslow depth (<1 mm vs >4 mm). Likewise, de Giorgi et al⁴² used both IHC staining and reverse transcriptase-polymerase chain reaction to observe increasing loss of ER-beta expression with increasing depth of MM. In contrast, Zhou et al⁴³ found no significant differences in ER-beta receptor expression using IHC analysis between the MMs of pregnant women and age- and stage-matched nonpregnant controls. There were also no associations between ER-beta expression and Breslow depth, tumor site, primary tumor or metastasis, disease stage at diagnosis, or survival.

In summary, while there is suggestion of an association between ER-beta expression and melanocytic lesions, the clinical relevance in MM and PAMM remains unclear. Some investigators still consider MM to be a hormone-sensitive malignancy, and suggest that estrogen along with other hormones, such as androgens, may have complex and overlapping roles in the behavior of MM.⁷

COUNSELING PATIENTS CONCERNING FUTURE PREGNANCY AND HORMONE THERAPY

Key points

- Oral contraceptive use in a patient previously diagnosed with melanoma does not appear to negatively influence prognosis

- **There is no compelling evidence to withhold hormone replacement therapy when medically necessary in a patient previously diagnosed with melanoma**

Case reports and case series have predicted a poorer prognosis for women diagnosed with MM during pregnancy, and skin pigmentation changes during pregnancy suggest a potential negative influence of pregnancy on melanoma progression. Immunologic changes during pregnancy, such as the proliferation of Tregs and uNKs, and a shift toward a T_H2 environment may promote a tolerogenic state similar to that seen in malignancy. However, the clinical and laboratory evidence at this time does not support an adverse influence of hormones on MM. The preponderance of evidence suggests that MM diagnosed before, during or after pregnancy does not affect prognosis. Some MMs diagnosed during pregnancy have an increased Breslow depth, which may be caused by a delay in diagnosis. The majority of evidence suggests no significant difference in primary tumor depth or anatomic location of MMs diagnosed in the pregnant woman compared to MMs in the nonpregnant woman.

In conclusion, women of child-bearing age diagnosed with MM should be advised about future pregnancies based on established prognostic factors, such as the primary tumor's Breslow thickness, ulceration, mitotic rate, and overall stage of disease. Future pregnancies are not contraindicated in women diagnosed with localized MM. If a patient has poor prognostic factors, it may be prudent to consider a delay of 3 years before the next pregnancy, because this is the time period in which recurrence of MM is most likely. The critical issue is the likelihood of the patient's survival through pregnancy and ability to raise her child. This should be discussed with the patient and her family and handled on a case by case basis. Other relevant factors include maternal age, because a delay in conception could create infertility issues. In addition, if MM recurs during subsequent pregnancy, there is risk of metastatic disease involving the fetus. However, overall the risk for the fetus is low, unless the mother has widely metastatic disease.²⁸

Based on epidemiologic studies, the use of OCPs in a patient previously diagnosed with MM does not appear to negatively influence prognosis. Much less is known about HRT, but there is no compelling evidence to withhold this therapy when medically necessary. Laboratory research concerning hormones and MM suggests that

ER-beta receptors are expressed in MMs, but the clinical relevance of ER-beta expression in MMs remains unclear.

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Understanding photodermatoses associated with defective DNA repair



Syndromes with cancer predisposition

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Learning objectives

After completing this learning activity, the participant should be able to describe the malignancies (both cutaneous and noncutaneous) associated with each genodermatosis; discuss the screening/management practices for photosensitive genodermatoses and describe appropriate methods of photoprotection and chemoprevention for cutaneous malignancies.

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Hereditary photodermatoses are a spectrum of rare photosensitive disorders that are often caused by genetic deficiency or malfunction of various components of the DNA repair pathway. This results clinically in extreme photosensitivity, with many syndromes exhibiting an increased risk of cutaneous malignancies. This review will focus specifically on the syndromes with malignant potential, including xeroderma pigmentosum, Bloom syndrome, and Rothmund–Thomson syndrome. The typical phenotypic findings of each disorder will be examined and contrasted, including noncutaneous identifiers to aid in diagnosis. The management of these patients will also be discussed. At this time, the mainstay of therapy remains strict photoprotection; however, genetic therapies are under investigation. (J Am Acad Dermatol 2016;75:855–70.)

Key words: Bloom syndrome; carcinogenic syndrome; nucleotide excision repair; photodermatoses; photosensitivity; Rothmund–Thomson; xeroderma pigmentosum.

Hereditary photodermatoses are characterized by an increased sensitivity to sunlight caused by a genetic defect. Most are autosomal recessive and manifest during infancy. While relatively rare, this spectrum of DNA repair–deficiency disorders is linked in some cases with early development of cutaneous and internal malignancies. Early recognition and diagnosis is

crucial to prevent actinic injuries that can lead to cutaneous malignancies. The first article in this continuing medical education series highlights genetic syndromes with associated carcinogenic potential (summarized in Tables I and II). The second article in this series focuses on genetic syndromes with photosensitivity but without associated malignancies.

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Abbreviations used:

6-4PP:	(6-4) pyrimidine-pyrimidone photoproduct
BCC:	basal cell carcinoma
BER:	base excision repair
CPD:	cyclobutane pyrimidine dimer
DSC:	De Sanctis—Cacchione
ERCC:	excision repair cross-complementing
NER:	nucleotide excision repair
PCNA:	proliferating cell nuclear antigen
ROS:	reactive oxygen species
RECQL:	RecQ-like
RTS:	Rothmund—Thomson syndrome
SCC:	squamous cell carcinoma
TCR:	transcription-coupled repair
UV:	ultraviolet
XP:	xeroderma pigmentosum

NUCLEOTIDE EXCISION REPAIR**Key points**

- Defects in the nucleotide excision repair pathway can result in photosensitivity and, in some cases, an increased incidence of skin cancer
- Cyclobutane pyrimidine dimers, 6-4 pyrimidine-pyrimidone photoproducts, and Dewar isomers are examples of DNA damage caused by ultraviolet radiation
- Lesions that significantly alter the double stranded helix of DNA are detected and repaired by a variety of proteins that, when mutated, result in deficient DNA repair and subsequently clinical disease

Ultraviolet light–induced damage to the genome

Living organisms on Earth are exposed to radiation emitted by the sun and have evolved to take advantage of sunlight, both for photosynthesis in plants and for photochemical synthesis of vitamin D in mammals. However, molecular damage in cells can occur after exposure to solar radiation, particularly that in the ultraviolet (UV) light range. UV radiation is divided into 3 spectral regions: UVC, UVB, and UVA.

UVC (100-290 nm). UVC light is the most harmful UV light, but it is filtered by atmospheric dioxygen and the ozone layer and therefore, does not reach the Earth's surface.

UVB (290-320 nm). UVB light is attenuated by the ozone layer, but the fraction that reaches the Earth's surface is sufficient to affect all life forms. UVB light comprises 5% of UV light that reaches the Earth's surface. The primary targets of UVB light are DNA and RNA, and the primary products are cyclobutane pyrimidine dimers (CPDs), 6-4 pyrimidine-pyrimidone photoproducts (6-4PPs), and Dewar

isomers (Fig 1), which can form between adjacent pyrimidines in nucleic acids.

UVA (320-400 nm). Ninety-five percent of UV light that reaches the Earth's surface is UVA light. UVA light interacts with proteins and other biomolecules, resulting in the generation of reactive oxygen species (ROS) and oxidation of DNA bases.^{3,4} It has also been shown to induce CPD (but not 6-4PP) formation.⁵ CPDs generated hours after exposure to UVA light have recently been ascribed to excitation of melanin by a combination of UVA-induced ROS and nitrogen species.⁶

CPDs and 6-4PPs are repaired in DNA via the nucleotide excision repair (NER) pathway, which appeared early in evolution and exists across the entire range of life forms, from unicellular bacteria to plants and humans. Oxidized bases in DNA are repaired by the base excision repair pathway. There are currently no human syndromes for which photosensitivity is caused by deficient repair of oxidized DNA bases. Although NER-deficient human cell lines have been reported to be hypersensitive to ROS,^{7,8} mutation spectra analyses in skin tumors from patients defective in NER reveal that essentially all mutations had been caused by CPD or 6-4PP.⁹

Nucleotide excision repair in humans

NER in eukaryotes (Fig 2) has been the subject of extensive reviews.¹⁰⁻¹² This versatile mechanism removes a large variety of helix-distorting lesions and structures from the genome.

The spectrum of human disorders resulting from mutations in NER proteins has been presented in several recent reviews.¹³⁻¹⁸ These inherited diseases are recessive, and therefore their incidence is highest among isolated populations with high rates of intermarriage.

DEFECTIVE NUCLEOTIDE EXCISION REPAIR PATHWAY AND CANCER: XERODERMA PIGMENTOSUM**Key points**

- Xeroderma pigmentosum is comprised of 8 nucleotide excision repair–deficient complementation groups, with groups A, C, and D being the most common
- Xeroderma pigmentosum variant is the result of a defective DNA polymerase η
- Photosensitivity is the most common presenting sign of xeroderma pigmentosum and is often evident during infancy
- Patients with xeroderma pigmentosum can have cutaneous, ocular, neurologic, and cognitive abnormalities, with an increased incidence of cutaneous and internal malignancies

Table I. Summary of photodermatoses with cancer predisposition associated with defective nucleotide excision repair, translesion synthesis, or RecQ-like helicases

Disease	Main clinical features	Action spectrum	Inheritance	Associated gene/cellular defects
Xeroderma pigmentosum	High photosensitivity, high incidence of skin cancer, ocular, neurologic, and cognitive abnormalities in some cases	290-340 nm	Autosomal recessive	<i>XPA, XPB, XPC, XPD, XPE, XPF, XPG</i> , and pol η -cells defective in nucleotide excision repair or in translesion synthesis; hypersensitive to UV light and bulky chemicals
Bloom syndrome	Erythema, telangiectasia, proportionate dwarfism, and increased internal cancers	Unknown	Autosomal recessive	<i>BLM</i> -quadriradial chromosomes; cells sensitive to ionizing radiation and alkylating agents
Rothmund-Thomson syndrome	Acute photosensitivity, poikiloderma, juvenile subcapsular cataracts, skin cancer, and osteosarcoma	Unknown	Autosomal recessive	<i>RTS</i> -cells sensitive to ionizing radiation

UV, Ultraviolet.

Table II. Photosensitivity caused by defects in DNA processing in humans

Function or pathway	Protein	HUGO, other nomenclature	Disease(s)	Photosensitivity	Cancer predisposition	Neurologic abnormalities
NER	XPA		XP	+++	+++	+++
	XPB	ERCC3	XP, XP/CS, and COFS syndrome	+++	+++	+++
	XPC		XP	+ to ++	+++	Rare
	XPD	ERCC2	XP, TTD, XP/CS, XP/TTD, and COFS syndrome	+ to +++	- to +++	>50%
	XPE	DDB2	XP	+ to ++	+	Rare
	XPF	ERCC4	XP, XFE, XP/CS, and FA	+ to +++	+	+ to +++
	XPG	ERCC5	XP and XP/CS	+ to +++	+ to +++	- to +++
	ERCC1	ERCC1	XFE, COFS syndrome, and CS	+ to +++	+	+++
	TTDA		TTD	+ to +++	-	+++
	CSA	ERCC8	CS and UV ^S S	+++	-	+++
TCR	CSB	ERCC6	CS, UV ^S S, DSC, and COFS syndrome	+++	-	+++
	UVSSA	KIAA1530	UV ^S S	+++	-	-
TLS	Pol η		XPV	+++	+++	Rare
	RecQ-like helicase	BLM	Bloom syndrome	Telangiectasia	++	- to ++
	RTS	RECQL3	Rothmund-Thomson	Erythema and telangiectasia	++	- to +

COFS, Cerebro-oculo-facial-skeletal; CS, Cockayne syndrome; DDB2, DNA damage-binding protein 2; FA, Fanconi anemia; HUGO, Human Genome Organization; NER, nucleotide excision repair; TCR, transcription-coupled repair; TLS, translesion synthesis; TTD, trichothiodystrophy; UV^SS, ultraviolet-sensitive syndrome; XP, xeroderma pigmentosum; XFE, XPF-ERCC1 progeroid syndrome.

Overview

Xeroderma pigmentosum (XP) is defined by the atrophic, dry, parchment-like texture of the skin, and by its high incidence (≤ 4000 -fold more prevalent in patients with XP than in unaffected individuals), and by the early development of tumors of the skin and sun-exposed areas. The disease is

comprised of 7 complementation groups, A to G, with defects in various steps of the NER pathway (Table III; Fig 2). The eighth group, XP variant (XPV), has normal repair of photoproducts but a defective DNA polymerase η (pol η), which has a role in DNA translesion synthesis over UV-induced photoproducts (Table III). Pol η copies DNA

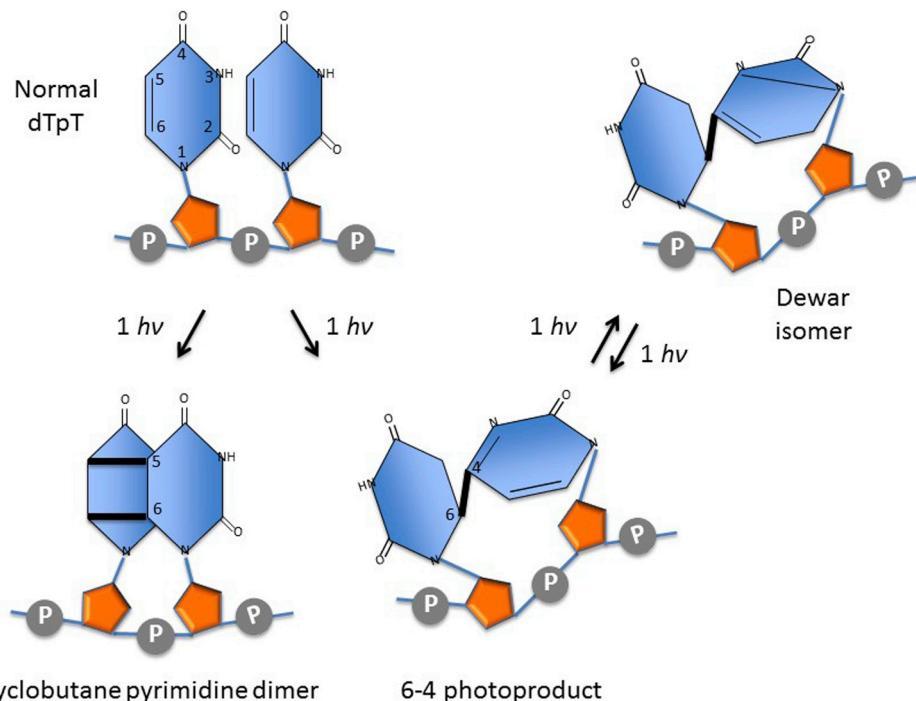


Fig 1. DNA photoproducts formed by ultraviolet (UV) light radiation. Absorption of UV photons ($h\nu$) by double bonds in pyrimidines results in the formation of cyclobutane pyrimidine dimers via energy-induced cycloaddition. 6-4 Photoproducts form by linkage of the C6 position of the 5' pyrimidine to the C4 position of the 3' pyrimidine, causing a significant distortion because of the almost perpendicular rotation of the pyrimidine planes with a resulting 87° angle.¹ 6-4 Photoproducts may undergo a secondary photoreaction to generate highly mutagenic Dewar isomers, formed by linking of the 2 nitrogen atoms in the heterocyclic ring of pyrimidines.² *dTpT*, Adjacent thymidines.

containing CPD with remarkably high fidelity, while it is exceedingly error prone when replicating undamaged DNA. XPV patients are also highly prone to skin cancer; lacking pol η , translesion synthesis is carried out by other polymerases (of which there are several in humans) that introduce mutations that can lead to malignancy.

Epidemiology

XP is an autosomal recessive disorder. The reported incidence in Japan is 1 in 20,000 to 40,000 live births, and in the United States and Europe is 1 in 250,000 to 1,000,000 live births.¹⁹ Men and women are affected equally, and XP has been reported in all races—albeit with a slightly lower frequency in darker-skinned populations.¹⁹ Complementation groups A, C, and D are the most common, with XPA particularly more prevalent in Japan and XPC more prevalent in Europe and the United States.^{20,21} Considerable phenotypic variability exists both between and within each complementation group, but overlapping features do exist.

Clinical manifestations

XP is predominantly characterized by cutaneous and ocular abnormalities that are typically found on sun-exposed sites; in some cases, these abnormalities are accompanied by various neurologic findings. Cutaneous involvement is generally evident by 2 years of age, with photosensitivity being the most common initial presenting sign (Fig 3, A-D).^{20,21} The action spectrum ranges from 290 to 340 nm. In 50% of patients, exaggerated sunburning—often with blistering and persistent erythema that lasts for weeks—may occur after minimal UV exposure.²⁰ Patients with more severe photosensitivity have a higher risk of developing neurologic dysfunction, and those in complementation groups A, B, D, F, and G may have excessive acute photosensitivity, while those with C, E, and XPV do not.^{23,24} Freckling is seen usually within the first year or two of life in all complementation groups. Dyspigmentation ranges from light brown to black macules, hypopigmented macules, and telangiectasias, resulting in poikilodermatous skin.^{20,24} Abnormal pigmentation may also be noted on mucous membranes. Additional cutaneous findings include premature photoaging,

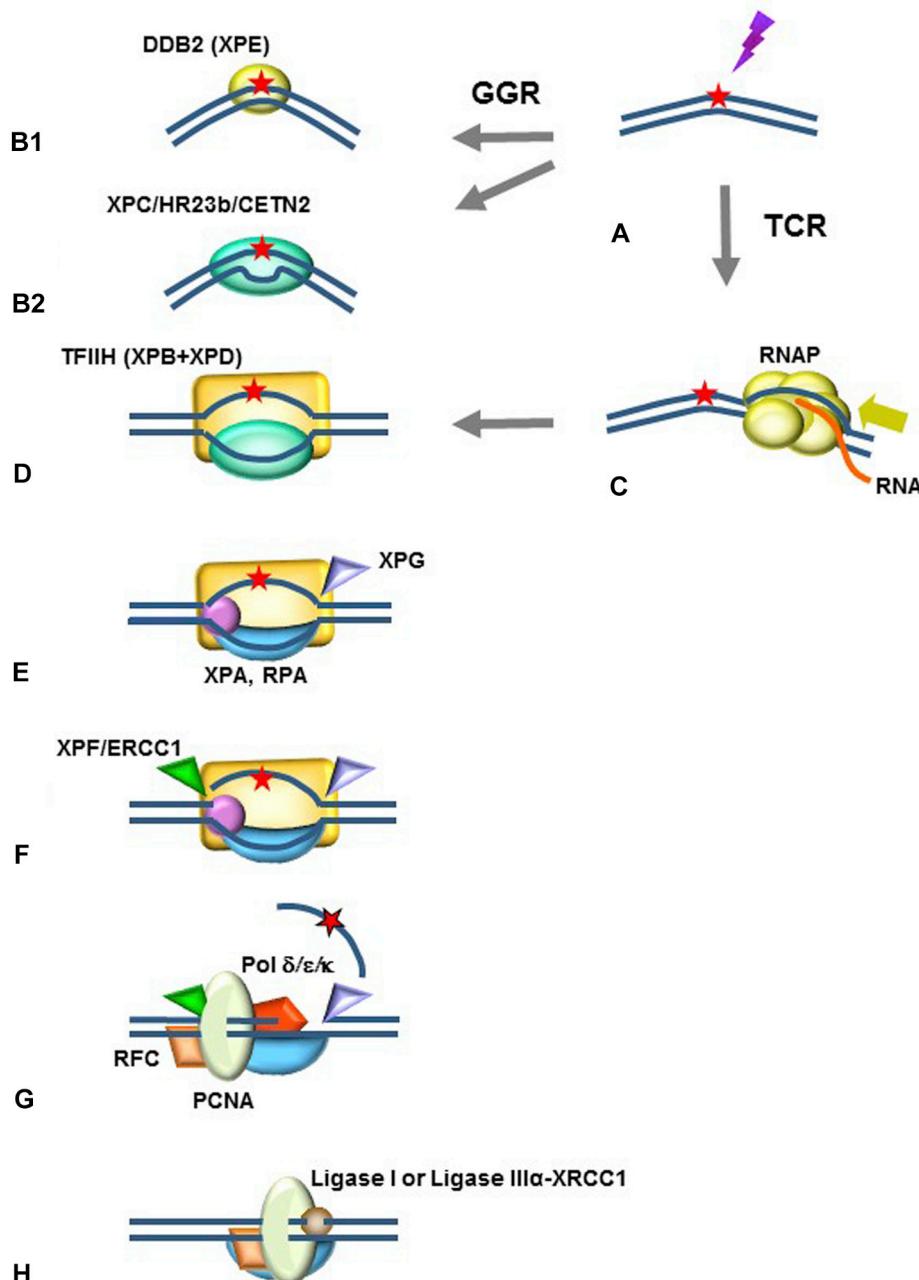


Fig 2. Nucleotide excision repair (NER). Xeroderma pigmentosum (XP) proteins, along with several other factors, play key roles in NER. The first step is recognition of the abnormal structure in DNA by XPC in complex with hRAD23b (HR23b) and centrin 2 (CETN2); in some cases, the lesion is detected first by DNA damage-binding protein 2 (DDB2; also known as XPE) (**B1** and **B2**). This group of enzymes operates throughout the genome in the global genomic repair (GGR) subpathway of NER. Alternatively, a lesion in DNA results in transcription arrest, which triggers the transcription-coupled repair (TCR) subpathway of NER, initiated by blocked RNA polymerases (RNAPs), which are described in the second article in this series (**A** and **C**). The 2 subpathways converge, and transcription factor IIH is recruited to the repair site (**D**). Unwinding of the DNA strands is carried out by the XPB helicase, 1 of 10 factors that constitute transcription factor IIH, creating a 20- to 30-nucleotide bubble around the lesion, termed preincision complex (**E**). XPA binds the 5' side of the bubble, and replication protein A (RPA) binds and protects the DNA strand opposite the lesion. The XPF/ERCC1 endonuclease makes the first incision at the 5' end of the complex (**F**), followed by repair synthesis by DNA polymerases δ , ϵ , and κ , proliferating cell nuclear antigen (PCNA), and replication factor C (RFC; **G**). This is followed by a second incision by XPG at the 3' end and removal of the oligonucleotide containing the lesion (**F** and **G**). Sealing the DNA strands by ligase I in replicating cells or ligase III α -XRCC1 in quiescent cells completes the repair (**H**).

Table III. Xeroderma pigmentosum complementation groups

Group	GRG	TCR	Protein	Protein function
A	—	—	XPA	Verification and positioning of the repair complex
B	—	—	XPB and ERCC3	TFIIP helicase and adenosine triphosphatase
C	—	+	XPC	Recognition, initial opening of the strands (complex with hRAD23b, centrin 2)
D	—	—	XPD and ERCC2	TFIIP helicase
E	—	+	XPE and DDB2	Recognition
F	—	—	XPF and ERCC4	Endonuclease (complex with ERCC1)
G	—	—	XPG and ERCC5	Endonuclease
Variant	+	+	Pol η	Translesion DNA polymerase
ERCC1	—	—	ERCC1	Endonuclease (complex with XPF)

DDB2, DNA damage-binding protein 2; Pol η , DNA polymerase η ; ERCC, excision repair cross-complementing; GRG, global genomic repair; TCR, transcription-coupled repair; TFIIP, transcription factor IIP; XP, xeroderma pigmentosum.

excessive dryness with parchment-like texture, atrophy, and scarring.

Ocular abnormalities occur in 40% of patients with XP, although recent evidence suggests this may be a gross underestimation (Fig 3, C).²⁵ Findings are often confined to areas exposed to UV radiation, such as the eyelids, conjunctiva, and cornea, with ocular malignancies displaying a similar distribution.^{26,27} Involvement typically occurs by 4 years of age.²⁵ One of the earliest changes is photophobia, followed by photoinduced conjunctival injection. UV radiation imparts much greater damage on the thinner eyelid tissue, resulting in entropion or ectropion or, in severe cases, complete loss of the lid.²⁸ Corneal opacity and neovascularization may lead to blindness.²⁷ Other ocular findings include corneal sicca, exposure keratitis, pterygium, blepharitis, conjunctival melanosis, and cataracts.^{25,26} Ocular neoplasms occur in approximately 11% of patients and include epithelioma, basal cell carcinoma (BCC), squamous cell carcinoma (SCC), and melanoma.^{26,29} Patients with the acute cutaneous sunburning phenotype are less likely to develop conjunctival melanosis and ectropion, but are at a higher risk of developing ocular surface malignancies when compared to nonburning patients.²⁵

The frequency of neurologic problems varies among the complementation groups, with >50% of patients with XPD having neurologic symptoms^{22,30}; such manifestations are rare in patients with XPC. Progressive neuronal and cognitive dysfunction often manifests as any combination of mental retardation, spasticity, ataxia, blindness, sensorineural deafness, peripheral neuropathy, gait disturbance, and microcephaly (Fig 3, D).^{18,31,32} The earliest neurologic clinical abnormalities are absent deep tendon reflexes and high-frequency hearing loss.²⁴ In severe cases, progression to slurred speech, loss of the ability to walk, and difficulty swallowing have

been reported. XP patients with neurologic degeneration have a higher mortality compared to those without, with death typically occurring in the third and fourth decades of life.^{22,24}

De Sanctis–Cacchione (DSC) syndrome was first described in 1932 with features of XP, mental deficiency, microcephaly, dwarfism, and gonadal hypoplasia with progressive neurologic degeneration.^{33,34} This is an extremely rare presentation, with cutaneous manifestations beginning earlier and being more severe compared with other XP phenotypes.³⁴ Fewer than 40% of patients with severe manifestations survive beyond 20 years of age.³⁵ The cause of death is typically related to neurologic complications and infections.^{33,34} Leukemia has also been a reported cause of death.³³

Recently, 2 patients with mutations in the gene encoding for excision repair cross-complementing 1 (ERCC1) protein had clinical features of XP in addition to those of Cockayne syndrome.^{36,37}

XP may also result in mucosal changes and increased oral malignancies.³⁸ The lips and tip of the tongue may show atrophy and telangiectasia, because these areas are thought to have a higher rate of UV light exposure compared to other mucosal sites.^{27,38} XP patients <20 years of age have an estimated 3000- to 10,000-fold increased risk of malignancies on the anterior third of the tongue.³⁸ The most common intraoral tumors include SCC and, rarely, angiosarcoma.^{38,39} This location is unique to patients with XP; mucosal SCC in healthy individuals occurs more commonly on the posterolateral surface and base of the tongue.

Patients with XP who are <20 years of age have a 10,000-fold increased risk of developing nonmelanoma skin cancers and a 2000-fold increase in melanoma when compared to the general population.^{24,40} The median age of first nonmelanoma skin cancer in patients with XP is 9 years, and the median



Fig 3. Xeroderma pigmentosum (XP). **A**, A 9-month-old with XPD with erythema and scaliness on the malar area after minimal sun exposure. The forehead was spared by a hat worn during sun exposure. **B**, A 2-year-old patient with XPC with multiple hyperpigmented macules on her face, squamous cell carcinoma or keratoacanthoma on the upper lip, and a clinically premalignant lesion on the forehead. **C**, A 23-year-old patient from Northern Africa with XPC with hyperpigmented macules on his face, basal cell carcinoma on the left side of the nasal bridge, and pigmented basal cell carcinoma on his left cheek. Corneal scarring was noted from unprotected sun exposure. **D**, A 35-year-old patient with XPA with hyperpigmented macules on sun-exposed areas and sensorineural deafness requiring the use of a hearing aid. (Courtesy of K. Kraemer, MD, from National Institutes of Health public access author manuscript; published in Bradford et al.²²)

age of the first melanoma is 22 years.²⁴ Patients with severe burning reactions in infancy (groups A and D) had a later onset of skin cancer development compared to their tanning counterparts (groups C and E), suggesting that early photoprotection initiated for the symptomatic groups resulted in decreased total UV radiation exposure. There are reports of atypical fibroxanthoma, basosquamous carcinoma, malignant fibrous histiocytomas, fibrosarcomas, and angiosarcomas, which are typically found in the elderly population, suggesting these are a result of UV-induced *p53* mutations.⁴¹ The nevi and melanomas in patients with XP have a higher frequency of UV-type mutations in the *PTEN* tumor suppressor gene with activation of the mammalian target of rapamycin pathway, and lower rates of *BRAF*, *NRAS*, and *KIT* mutations compared to melanomas in the general population.⁴² This again reinforces the role of UV damage and skin cancer in these patients. The incidence of internal malignancies in patients with XP is increased 10- to 20-fold, and even 50-fold for neurologic malignancies.^{19,36} Typical internal malignancies include brain, colon, and lung cancers and leukemia.^{27,37,40,43} While the exact mechanism for this increased carcinogenesis in sun-protected organs remains unclear, it is hypothesized, particularly for neurologic neoplasms, that oxidative DNA damage generated through metabolism or other sources might result in DNA damage that cannot be adequately repaired, leading to malignancy or progressive neuronal death.³⁶ Emerging data also suggest that specific genetic polymorphisms in this population contribute to an increased genetic susceptibility to chemical carcinogenesis.⁴⁴⁻⁴⁶

Combined phenotypes

Certain mutations in XP genes may result in combined phenotypes (eg, XP/Cockayne syndrome or XP/trichothiodystrophy), different disorders (eg, XPF-ERCC1 progeroid syndrome),⁴⁷ severe and progressive neurodegeneration,⁴⁸ or Cockayne syndrome.⁴⁹ Some mutations in *XPF* (*ERCC4*) result in Fanconi anemia alone⁵⁰ or in combination with XP and Cockayne syndrome,⁴⁹ and individuals with these mutations belong to the FancQ complementation group of FA.⁵⁰

Diagnostic evaluation

Most clinical presentations are sufficiently characteristic, and the diagnosis is typically based on history and physical examination alone. Molecular diagnostic methods include the measurement of unscheduled DNA synthesis in UVC-exposed cells from patients.²⁹ Complementation analysis to identify affected genes may also provide insight into the

diagnosis.²⁹ Prompt diagnosis and rapid initiation of strict photoprotection is key to reducing the risk of malignancy.¹⁹

Management

There is no cure for XP, and management is therefore directed at the prevention of malignancies and ocular damage with lifelong rigorous photoprotection, which is addressed in the second article in this series.

The average age of death of patients with XP is 32 years; however, with increasing awareness and prompt diagnosis and management, lifespans will hopefully increase.⁵¹ To achieve this goal, multi-specialty clinics and support groups are essential to facilitate the monitoring and management of this disease. Frequent eye examinations, skin examinations with prompt removal of precancerous lesions, routine audiometry testing, head circumference measurements, and gait and deep tendon reflex testing to screen for neurologic abnormalities are advocated.²⁹ Topical T4 endonuclease V in a liposomal delivery vehicle has been reported to reduce the development of BCCs and actinic keratoses in this patient population.^{52,53} Genetic therapies are currently under investigation, focusing on the genetic correction of epidermal stem cells *in vitro* followed by the production of genetically normal epidermal sheets and subsequent patient grafting.⁵⁴

Oral isotretinoin has shown success in a few cases when combined with chemotherapy for unresectable SCCs.⁵⁵ In addition, oral isotretinoin (0.5-2 mg/kg/d) has been used as a preventative agent in patients with XP; some studies have found a two-thirds diminution in the rates of development of skin cancers.⁵⁶ Oral retinoids must be continued indefinitely to maintain their effectiveness; their use is generally limited because of side effects, particularly in children.⁵⁷

Radiation therapy for high-risk SCCs has been reported with some success. In 1 small case study with 7 years of follow-up, there were fewer noted skin cancers in the radiation-treated region.⁵⁸ This suggests a normal clinical response to ionizing radiation and a specificity of the NER defect to UV radiation-induced damage. However, more data are needed to better elucidate long-term safety in this population.^{58,59}

DEFECTS IN DNA HELICASES

DNA helicases unwind the DNA double helix to provide single-stranded DNA when needed for replication, transcription, repair, and recombination. There are 5 human RecQ-like (RECQL) homologs of the *RecQ* gene from *Escherichia coli*, which codes for

Table IV. Human RecQ-like DNA helicases

Proteins	Diseases	Photosensitivity	Cancer	Protein function
RECQL1	—	—	+++*	Initiation of replication
RECQL2, WRN	Werner syndrome	—	+++	Resolution of gene conversion events
RECQL3, BLM	Bloom syndrome	Telangiectasia	+++	Resolution of Holliday junctions
RECQL4, RTS	Rothmund–Thomson syndrome	30% of patients	+++	Initiation of replication repair synthesis in
	RAPADILINO	—	+++	nucleotide excision repair ⁶⁰
	Baller–Gerold syndrome	Poikiloderma	?	
RECQL5	—	—	+++*	Control of transcription elongation ⁶¹

RAPADILINO, Radial ray malformations, patella and palate abnormalities, diarrhea and dislocated joints, limb abnormalities and little size, and slender nose and normal intelligence.

*Cancer propensity has been found in animal models. Mutations in genes encoding for these proteins appear frequently in human tumors.

a DNA helicase with 3' to 5' directional specificity involved in recombination and repair of DNA breaks (Table IV).

Mutations in 3 of the genes, *RecQL2* (*WRN*), *RecQL3* (*BLM*), and *RecQL4* (*RTS*), have been associated with Werner, Bloom, and Rothmund–Thomson syndromes (*RTS*), respectively. Only Bloom syndrome and *RTS* present with photosensitivity. Patients with Werner syndrome have premature aging and early-onset sarcomas and mesenchymal tumors, but photosensitivity has not been reported. Mutations in *RECQL1* and *RECQL5* have not yet been genetically linked to a disease.⁶² Roles in telomere maintenance have been suggested for these 2 helicases.⁶³

Bloom syndrome (congenital telangiectatic erythema)

Key points

- Bloom syndrome results from mutations in the *BLM* gene, which encodes for the *RECQL3* DNA helicase
- Cutaneous features of Bloom syndrome commonly include early-onset photoinduced erythema and telangiectasias on the cheeks, hands, and forearms
- Noncutaneous findings often include “proportionate dwarfism,” high-pitched voices, oversized ears, long limbs, and susceptibility to various infections
- Patients with Bloom syndrome have an increased incidence of malignancy involving almost all major organ systems; cutaneous neoplasms are fairly uncommon
- A quadriradial configuration in chromosomes is pathognomonic for this syndrome

Epidemiology. Bloom syndrome is a rare chromosomal breakage disease resulting from mutations in the *BLM* gene, which encodes for the *RECQL3* BLM DNA helicase. This autosomal recessive disorder of photosensitivity, first reported in 1954,⁶⁴ is

most prevalent among the Ashkenazi Jewish population of Eastern Europe and Israel, with a reported prevalence rate of approximately 1 in 48,000 persons.⁶⁵ It has also been described in Japanese and Indian patients.^{66,67} Males and females are affected at a 1.4:1 ratio.⁶⁴

Clinical manifestations. Patients have photoinduced erythema and telangiectasias within the first few weeks of life, typically involving the malar cheeks (“butterfly” distribution), ears, eyelids, dorsal aspects of the hands, and forearms.^{64,68} The action spectrum of photosensitivity remains unknown. Additional cutaneous findings include café-au-lait macules with adjacent areas of hypopigmentation, poikiloderma (Fig 4, A), and photosensitivity leading to cheilitis, fissuring, burning, and blistering on sun-exposed regions.⁶⁹ Clinically and histologically, these cutaneous findings may closely resemble lupus erythematosus; however, direct immunofluorescence studies fail to reveal linear immunoglobulin deposits at the dermoepidermal junction, as seen in patients with lupus.⁷⁰ Cutaneous problems may improve after puberty, making the diagnosis even more challenging.²⁰

Patients typically have severe pre- and postnatal growth retardation resulting in short stature, disproportionately small head circumference compared to height (dolichocephaly), and reduced subcutaneous fat content while maintaining normal muscle development.^{64,68,69} Patients tend to remain below the third percentile for height and weight and have been described as having “proportionate dwarfism.”^{21,64} They have high-arched palates (resulting in high-pitched voices), oversized ears, and long facies with a prominent nose and small jaw, often referred to as “bird-like” features.^{64,69} Their limbs are long with large hands and feet. Learning disabilities are not unusual, but intelligence is generally normal.⁷¹ Type II diabetes is often seen with development at a young age.⁶⁸ Reduced levels of serum immunoglobulin M and immunoglobulin A have been reported, rendering patients susceptible to various

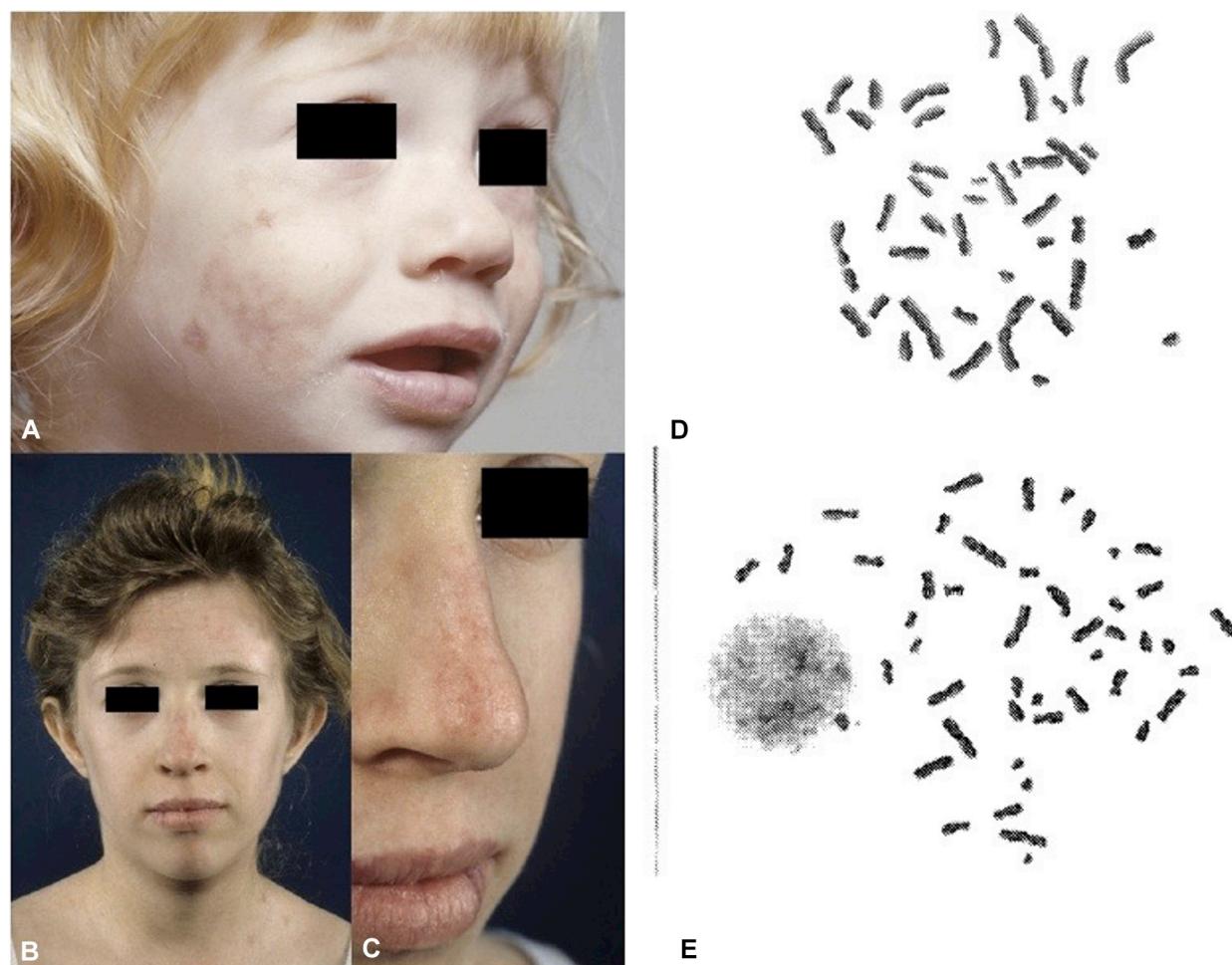


Fig 4. Bloom syndrome. **A**, A young child with a fair complexion with classic poikiloderma on her left cheek. **B**, A fair-skinned woman with poikiloderma on her forehead and (**C**) the dorsal surface of her nose. The right half of the figure is a sister chromatid exchange study. Lymphocyte chromosomes are cultured in bromodeoxyuridine for 2 generations and then stained with Giemsa stain. Chromatid DNA, which completely incorporates bromodeoxyuridine, appears gray. Partially incorporated bromodeoxyuridine appears black. If there is no exchange, 1 chromatid will be either entirely black or entirely gray. **D**, Control chromosomes. There are approximately 8 sister chromatid exchanges present. **E**, Chromosomes from an affected patient, with approximately 75 exchanges between sister chromatids. (**A-C**, Used with permission from Arora et al⁶⁹; **D** and **E**, used with permission from Gretzula et al.⁶⁴)

sinopulmonary and gastrointestinal infections, including otitis media, pneumonia, bronchiectasis, and chronic lung disease.^{64,69,72} Other associated features include infertility, clinodactyly, syndactyly, congenital heart disease, and annular pancreas.^{68,69,73} Ocular findings have rarely been described; however, there have been reported cases of conjunctival telangiectasias.^{65,71}

The most life-threatening feature of Bloom syndrome is the increased risk of malignancy, with a 150- to 300-fold risk compared to the general population.^{69,74} This is likely the result of a 10-fold increased rate of spontaneous sister chromatid

exchanges, resulting in chromosomal instability.^{69,75} Most major organ systems can be involved, including the hematologic system, upper and lower gastrointestinal tract, genitalia, urinary tract, liver, breast, lung, and skin.^{21,69} Brain tumors, retinoblastomas, and connective tissue sarcomas have also been reported.²¹ Leukemia is the most common cancer before 20 years of age, after which it shifts toward sarcomas and carcinomas.⁶⁹ While skin cancers are fairly uncommon in patients with Bloom syndrome, they have been reported with a mean age of development of 31.7 years. There may also be an underrepresentation of cutaneous malignancies in

this population because they typically die in the second and third decades of life, before skin cancers can fully develop.⁶⁹

Evaluation and diagnosis. A diagnosis of Bloom syndrome typically includes a combination of clinical features and chromosomal analysis. A quadriradial configuration in chromosomes from lymphocytes, defined as 4-armed chromosomes resulting from recombination from 2 homologous chromosomes, is pathognomonic for this disorder (Fig 4).^{64,69} Immunohistochemical detection of the BLM protein and identification of a mutated *BLM* gene or altered gene products are other less commonly used means of identification and diagnosis.⁶⁹ Screening is recommended among high-risk populations, such as the Ashkenazi Jewish community, using polymerase chain reaction studies, Southern/Northern blot analysis, or direct DNA sequence analysis.^{69,76}

Management. Regular physical examinations with an extensive review of systems should be conducted—especially of the hematologic system for patients <20 years of age. Radiation therapy and alkylating drugs should be avoided where possible, because these patients are highly susceptible to DNA-damaging therapies.⁶⁹ Patients should practice strict photoprotection. Infections should be treated promptly and diabetes managed appropriately. Dermatologic examinations are helpful in identifying café-au-lait macules, which have been associated with underlying systemic malignancies in these patients.⁷⁷

Rothmund–Thomson syndrome (poikiloderma congenitale)

Key points

- Rothmund–Thomson syndrome results from a mutation in the *RECQL4* helicase gene
- Acute photosensitivity begins in early infancy and eventually resolves with clinically evident poikiloderma
- One of the more distinguishing features is an increased incidence of juvenile subcapsular bilateral cataracts
- Aside from cutaneous malignancies, osteosarcoma is the primary form of cancer in this patient population

Epidemiology. RTS, also referred to as poikiloderma congenitale, is a rare autosomal recessive photosensitive genodermatosis caused by mutation of the *RECQL4* gene.¹⁷ It has been reported worldwide, across a variety of ethnicities including Asian, African, and Hispanic children.⁷⁸ Originally, RTS was

reported with a female predominance of 4:1; more recent evidence suggests a closer 1.4:1 female to male ratio, which is more in keeping with an autosomal recessive inheritance pattern.^{78–80} There have been about 300 cases reported in the literature.⁸¹

Clinical manifestations. Key features of this disease include erythematous patches with swelling and blistering on the cheeks and extremities after sun exposure starting in early infancy, initially excluding flexural areas and the trunk.^{17,21,79} About 89% of patients have skin changes within the first year of life, with 58% of these changes within the first 3 to 6 months, although cases of later onset have been reported.^{79,82} The acute photosensitive phase may last from a few months to a few years, and gradually evolves into a chronic phase with telangiectasia, dyspigmentation, and punctate atrophy manifesting as poikiloderma. Gradually, the eruption extends onto the extensor surfaces of the extremities and the trunk, abdomen, and buttocks, and persists into adulthood (Fig 5, A).^{78,79} While the poikiloderma is more exaggerated in sun-exposed areas, covered areas may also be affected and often appear as brown pigmentation.^{78,79} Phototesting in 1 adult patient showed photosensitivity in the UVA but not in the UVB range.⁸³

In addition to the photosensitivity, 80% of these patients suffer from partial or total alopecia, including sparse eyebrows and eyelashes.^{21,79} Unlike the poikiloderma, alopecia normally progresses into the second and third decades of life.⁷⁹ Palmoplantar keratoderma has been reported in up to one-third of cases, along with hyperkeratotic lesions (Fig 5, B).^{78–80,84} More variable features include nail abnormalities, hypogonadism or delayed sexual development, and gastrointestinal disturbances, such as chronic emesis or diarrhea.^{79,84,85} Additional gastrointestinal findings have been reported sporadically, such as esophageal or pyloric stenosis, anal atresia, annular pancreas, and rectovaginal fistula.^{80,86} Intelligence is typically normal, but some cases of mental retardation have been reported. Dental anomalies are also relatively common.^{21,79,87,88} Calcinosis cutis has also been rarely reported, with a single described case of calcinosis universalis.^{79,89}

One of the more distinguishing features of RTS is the increased incidence of juvenile cataracts.²¹ In 1 study, half of patients observed to at least 13 years of age developed cataracts, and 73% of those cases developed before 6 years of age.^{79,90} The cataracts are typically subcapsular, bilateral, and develop rapidly within a few short months. Other less common ocular abnormalities include exophthalmos,



Fig 5. Rothmund–Thomson syndrome. **A**, Erythema, scaliness, poikiloderma, and dyspigmentation in a patient with Rothmund–Thomson syndrome. **B**, Marked keratoderma of the soles. **C**, Note the absence of thumbs. (Courtesy of Tor A. Shwayder, MD, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.)

corneal atrophy, photophobia, blue sclera, and glaucoma.^{80,91}

Similar to Bloom syndrome, these patients have small stature. Up to 75% have radiologic bony abnormalities,⁹² including skeletal dysplasias, absent or malformed bones, or delayed bone formation. The most frequently reported skeletal abnormality is a typical facies with frontal bossing, saddle nose, and

prognathism.⁷⁹ Small hands and feet in proportion to body size is reported in 20% of patients, followed by absent or malformed radii. Additional abnormalities include absent or partially formed thumbs (Fig 5, C), syndactyly, club feet, abnormal ulnae, scoliosis, microcephaly, patellar ossification defects, and osteoporosis with pathologic fractures.^{79,80} While absent thumbs are considered a more classic feature, there

are also reports of other absent digits on the hands and feet.⁸⁵

These patients are at risk for developing cutaneous malignancies and osteosarcoma. Osteosarcoma occurs in about 30% of patients, with a median age of onset between 11 and 14 years of age, compared to the typical 17 years of age in the general population.^{78,80,93} Bony abnormalities exist before the development of malignancy, and the tibia and femur are the most common sites involved.^{79,80,88} In addition, multicentric osteosarcoma (tumor at ≥ 2 sites in the absence of pulmonary metastases) is more common in the RTS population compared to the general population.^{80,94,95} Screening is recommended with baseline long bone radiologic survey by 3 years of age, and dysplastic findings are followed yearly thereafter. Treatment of identified osteosarcoma involves a multimodal approach with surgery and chemotherapy; tumors are often resistant to radiation.⁹³ Other noncutaneous malignancies may occur, including bone fibrosarcoma, parathyroid adenoma, Hodgkin lymphoma, eccrine porocarcinoma, acute myelogenous leukemia, and gastric carcinoma.^{79,88,90} BCC, SCC, and melanoma have also been reported, most commonly by the third decade of life.^{80,95} Rarely, progressive leukopenia, chronic anemia, and even aplastic anemia, myelodysplasia, and leukemia have been reported.⁹⁶ The life expectancy of patients with RTS is normal if there is no development of malignancy. Those affected by osteosarcoma have a 5-year survival rate of 60% to 70%, similar to non-RTS patients with osteosarcoma.⁸⁰

Some researchers have divided RTS into 2 distinct subgroups: RTS-I, which is characterized by poikiloderma, ectodermal dysplasia, and juvenile cataracts, and RTS-II, which is characterized by poikiloderma, congenital bone defects, and a risk of osteosarcoma and cutaneous malignancies.^{80,97} RTS-II patients are thought to possess homozygous or compound heterozygous mutations in the *RECQL4* gene, while RTS-I patients are negative for the *RECQL4* mutation, and the exact etiology remains unidentified. Whether these are actually 2 distinct entities with overlapping features versus intersecting nosologic syndromes involving genes interacting on the same pathway is yet to be elucidated.⁸⁰

Mutations in *RECQL4* has been reported to be associated with 2 syndromes that are similar to RTS but without photosensitivity: RAPADILINO⁹⁸ (radial ray malformations, patella and palate abnormalities, diarrhea and dislocated joints, limb abnormalities and little size, and slender nose and normal intelligence; without poikiloderma) or Baller-Gerold⁹⁶ (with poikiloderma; Table IV).

Diagnosis. The diagnosis of RTS is typically established by the clinical presentation of photosensitive eruption combined with extracutaneous manifestations of skeletal anomalies and juvenile cataracts and skin cancers. RTS should be considered in all young patients with osteosarcoma, particularly if associated with abnormal cutaneous findings. Molecular testing for *RECQL4* mutations is available.²¹

Management. Strict photoprotection is essential to reduce the likelihood of developing cutaneous malignancies, and there should also be regular ophthalmologic examinations and appropriate screening for osteosarcoma. Bony abnormalities and cataracts are corrected surgically. A complete blood cell count with differential is also recommended to detect rare cases of associated hematologic abnormality. Facial telangiectasias can be successfully treated with vascular laser therapy.^{99,100} Treatment options for verrucous hyperkeratotic lesions include oral and topical retinoids and topical keratolytics.⁹⁰

Similar to patients with XP, there is a theoretical concern exposing patients with RTS to ionizing radiation. In vitro studies exposing *RECQL4*-deficient fibroblasts to ionizing radiation showed mixed results, with most suggesting enhanced sensitivity in this population.^{94,101-103} There are reports of successfully treated patients with radiotherapy for skin malignancies, although some showed increased radiosensitivity.^{104,105} Longer-term data are needed to fully elucidate the risk.

OTHER DISEASES WITH DEFECTIVE DNA REPAIR

The proliferating cell nuclear antigen (PCNA) is a highly conserved sliding clamp protein that is essential for DNA replication and repair. It has been dubbed a “tool belt” that recruits DNA synthesis enzymes and facilitates polymerase switching as needed for each task, including transitions between replicative polymerases and translesion synthesis polymerases when encountering DNA lesions.¹⁰⁶ Mutations in the *PCNA* gene that profoundly impair protein function would be incompatible with life. A syndrome with features that include short stature, hearing loss, premature aging, telangiectasia, neurodegeneration, and photosensitivity (of unknown action spectrum) resulted from a homozygous missense mutation in *PCNA* in 4 patients from an Amish family between 11 and 31 years of age. One of the patients (26 years of age) had a BCC. Whereas this mutation appeared to have no effect on protein functions or DNA replication, cells from these patients showed substantial reductions in both UV

survival and RNA synthesis recovery after exposure to UVC radiation in vitro.¹⁰⁷

In conclusion, hereditary photodermatoses comprise a group of rare, inherited photosensitivity disorders that are caused by a deficiency in adequate DNA repair mechanisms. XP, RTS, and Bloom syndrome—while clinically and genetically distinct—each carry an increased risk of carcinogenesis in addition to phenotypic photosensitivity. It is crucial that dermatologists understand and recognize these conditions in order to promptly and effectively initiate aggressive photoprotection and disease-appropriate screening and treatment to reduce morbidity and mortality.

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Understanding photodermatoses associated with defective DNA repair



Photosensitive syndromes without associated cancer predisposition

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Learning objectives

After completing this learning activity, the participant should be able to describe the basic structure of the nucleotide excision repair pathways and the genes involved; compare and contrast photosensitive genodermatoses; and identify the genes and their protein products that become mutated/malfunctioning leading to the development of photosensitive syndromes.

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Photodermatoses associated with defective DNA repair are a group of photosensitive hereditary skin disorders. In this review, we focus on diseases and syndromes with defective nucleotide excision repair that are not accompanied by an increased risk of cutaneous malignancies despite having photosensitivity. Specifically, the gene mutations and transcription defects, epidemiology, and clinical features of Cockayne syndrome, cerebro-oculo-facial-skeletal syndrome, ultraviolet-sensitive syndrome, and trichothiodystrophy will be discussed. These conditions may also have other extracutaneous involvement affecting the neurologic system and growth and development. Rigorous photoprotection remains an important component of the management of these inherited DNA repair-deficiency photodermatoses. (J Am Acad Dermatol 2016;75:873-82.)

Key words: cerebro-oculo-facial-skeletal syndrome; Cockayne syndrome; nucleotide excision repair; photodermatoses; photosensitivity; trichothiodystrophy; UV-sensitive syndrome.

The diseases described in this article differ from xeroderma pigmentosum (XP) and other diseases discussed in the first article in this series in that the patients, while photosensitive, are not abnormally cancer-prone (Table I). Affected individuals may have severe developmental and neurologic defects that are distinct from those observed in patients with XP.¹

TRANSCRIPTION-COUPLED REPAIR

Key points

- Defects in the transcription-coupled repair pathway can result in diseases with photosensitivity, but these patients are generally not cancer-prone
- The transcription-coupled repair mechanism detects any adducts that disrupt the

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Abbreviations used:

6-4PP:	(6-4) pyrimidine-pyrimidone photoproduct
COFS:	cerebro-oculo-facio-skeletal
CS:	Cockayne syndrome
CPD:	cyclobutane pyrimidine dimer
ERCC:	excision repair cross-complementing
NER:	nucleotide excision repair
RNAP:	RNA polymerase
TCR:	transcription-coupled repair
TFIIS:	transcription factor IIS
TTD:	trichothiodystrophy
UV:	ultraviolet
UV ^S S:	ultraviolet-sensitive syndrome
XP:	xeroderma pigmentosum

progression of RNA polymerases, activating protein complexes and transcription factors to bring about repair of the defects

- **Blocked RNA polymerase II constitutes the first step for damage recognition in the transcription-coupled repair pathway**
- **An arrested RNA polymerase II may be targeted for degradation; alternately, it may bypass the lesion with possible misincorporation of ribonucleotides, a phenomenon termed transcriptional mutagenesis**

In the process of RNA synthesis, a translocating RNA polymerase (RNAP) can be blocked by bulky adducts, such as the photoadducts cyclobutane pyrimidine dimers (CPDs) and 6-4 pyrimidine-pyrimidones (6-4PPs), cis-platin intrastrand cross-links, benzo[a]pyrene diol epoxide, and other polycyclic aromatic hydrocarbons; by discontinuities in the template strand (eg, nicks, gaps, and abasic sites); and by collisions with replication complexes. These complexes or defects can obstruct important metabolic processes, such as DNA replication; in mammals, they constitute a strong signal for apoptosis. Transcription-coupled repair (TCR) is a specialized mechanism for the detection and rapid removal of lesions that impede the progression of RNAP.

Blocked RNAPII constitutes the first step for damage recognition in TCR (Fig 1, A); there is no evidence to date for participation of human RNAPI, RNAPIII, or mitochondrial RNAP in TCR.^{2,3} The arrested elongation complex recruits Cockayne syndrome B (CSB; also known as excision repair cross-complementing group 6 [ERCC6]), a transcription elongation factor that translocates along template DNA with RNAPII.⁴ CSB recruits the CSA (ERCC8) complex, nucleotide excision repair (NER) factors, and chromatin remodeling factors, such as p300 and high mobility group nucleosome binding domain 1, to sites of arrested RNAPII, and has been

considered the master coordinator of TCR in humans.

There are several potential outcomes after RNAPII arrest. An arrested RNAPII may be targeted for degradation through neural precursor cell-expressed developmentally downregulated protein 4 (Nedd4)-dependent ubiquitination and proteosomal degradation (Fig 1, B). Alternately, an arrested RNAPII may bypass the lesion with possible misincorporation of ribonucleotides, a phenomenon termed transcriptional mutagenesis⁵ (Fig 1, C). Another proposed model is that the RNAPII reverses translocation with cleavage of the nascent transcript, also called backtracking, to reveal the offending lesion and to allow space for the repair complex to operate (Fig 1, D). Transcription factor IIS (TFIIS), a transcription elongation factor that stimulates mRNA cleavage by RNAPII, is recruited to sites of damage by CSA.⁶ Lastly, TCR might be initiated by remodeling⁷ the RNAPII without removal from the arrest site⁷ (Fig 1, E). Several protein complexes involved in chromatin remodeling, biogenesis of mRNA, and its export to the cytoplasm also participate in TCR (Table II).⁸

DISEASES WITH DEFECTIVE TRANSCRIPTION-COUPLED REPAIR
Cockayne syndrome**Key points**

- **Cockayne syndrome is a rare autosomal recessive disorder**
- **It comprises mainly 2 principal complementation groups, with mutations in the genes encoding Cockayne syndrome A and Cockayne syndrome B proteins (excision repair cross-complementing groups 8 and 6, respectively)**
- **Cells from patients with Cockayne syndrome are defective in the transcription-coupled repair subpathway of nucleotide excision repair**
- **Patients with Cockayne syndrome present with 3 major characteristics: microcephaly, stunted growth, and progressive neurologic dysfunction caused by leukodystrophy**
- **Cutaneous manifestations include photosensitivity, dry thin skin, dry hair, anhidrosis, and acral cyanotic livedo**
- **Patients do not develop sun-induced pigmentation and are not prone to ultraviolet light-related skin malignancies**

Background. Cockayne syndrome (CS) is a complex disease with a multitude of symptoms.

Table I. Summary of photodermatoses associated with defective nucleotide excision repair without cancer predisposition

Disease	Primary clinical features	Action spectrum	Inheritance	Associated gene/cellular defects
CS	Microcephaly, stunted growth, progressive neurologic dysfunction, dental caries, pigmentary retinopathy, cataracts, sensorineural hearing loss, cachectic dwarfism with stooped posture, and photosensitivity	UVB and visible light	Autosomal recessive	<i>ERCC8, ERCC6, ERCC4, and ERCC1</i> —cells defective in TCR; hypersensitive to UV light and agents that cause bulky DNA adducts, and to oxidizing chemicals; failure or delay to recover RNA synthesis after DNA damage
COFS syndrome	Microcephaly, cataracts, microphthalmia, arthrogryposis, severe developmental delay, postnatal growth failure, facial dysmorphism with prominent nasal root, overhanging upper lip, and photosensitivity	Unknown	Autosomal recessive	<i>ERCC6, ERCC1, ERCC2, and ERCC5</i> —similar to CS
UV-sensitive syndrome	Acute sunburn, dryness, freckling, pigmentation anomalies, and telangiectasias in sun-exposed skin	Unknown	Autosomal recessive	<i>ERCC8, ERCC6, and UVSSA</i> —cells defective in TCR; hypersensitive to UV light and agents that cause bulky DNA adducts; normal resistance to oxidizing chemicals; failure or delay to recover RNA synthesis after DNA damage
Trichothiodystrophy	Intellectual impairment, decreased fertility, short stature, microcephaly, osteoporosis, premature aging, proneness to infections, dental caries, hearing loss and cataracts. Photosensitivity, ichthyosis, brittle hair and nails.	UVB	Autosomal recessive	<i>XPB (ERCC3), XPD (ERCC2), and TTDA</i> —cells defective in GGR and TCR; reduced concentrations, increased instability, and abnormal function of TFIIH

COFS, Cerebro-oculo-facio-skeletal; CS, Cockayne syndrome; ERCC, excision repair cross-complementing group; GGR, global genomic repair; TCR, transcription-coupled repair; TFIIH, transcription factor IIH; UVB, ultraviolet B light; UVSSA, UV-stimulated scaffold protein A.

There are 2 principal complementation groups of CS, CSA and CSB, with mutations in genes encoding the CSA and CSB proteins (*ERCC8* and *ERCC*, respectively). Mutations in genes encoding for XP complementation group F (*ERCC4* and *ERCC1*) have also been found to cause CS.⁹ In rare cases, patients with mutations in the *XPB*, *XPD*, or *XPG* genes have a combination of symptoms of CS and XP, and mutations in *XPF* may result in a combined XP-CS-Fanconi anemia phenotype. A handful of CS patients remain unassigned to any of these genes.⁹

In vitro, cells from CS patients are defective in the TCR subpathway of NER, but they are proficient in the global repair of bulky DNA adducts and

ultraviolet C light-induced CPD and 6-4PP; moreover, it has recently been shown that CSB is required for TCR of the oxidized base 8-oxoguanine.¹⁰ It should be noted that the developmental and neurologic features of the disease might not be related to the TCR defect.¹¹ The CS phenotype may arise from abnormalities in transcription by RNAPII^{12,13} or by RNAPI with consequent ribosomal stress¹³; defects in other functions of transcription factor IIH (TFIIH), such as phosphorylation of nuclear hormone receptors, have also been suggested.¹⁴ The expression of genes involved in neuronal development is dysregulated in cells from patients with CS.¹⁵ CSB-deficient neuronal networks were also found

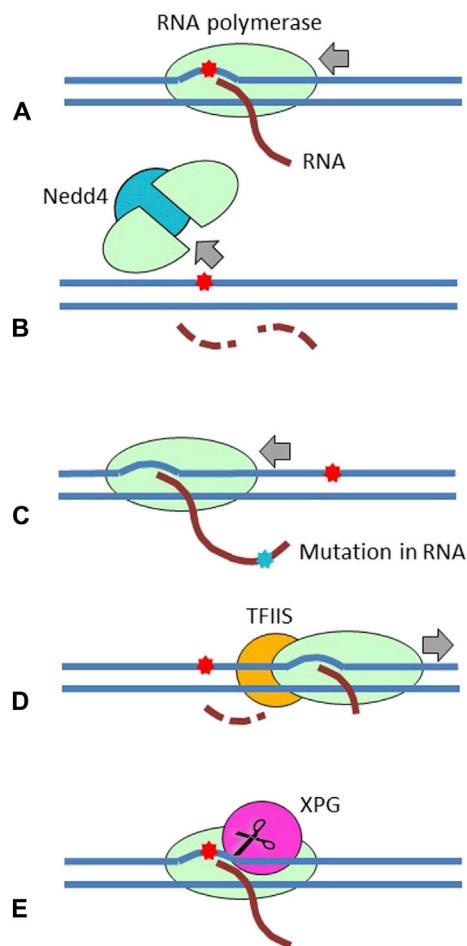


Fig 1. Potential outcomes after RNA polymerase II (RNAPII) arrest. **A**, Arrest of RNAPII at a lesion. Prolonged arrest activates cell cycle checkpoints that control the progression of cellular division and also may lead to apoptosis. **B**, Removal of the RNAPII from the DNA through neural precursor cell-expressed developmentally downregulated protein 4 (Nedd4)-dependent ubiquitination and proteasomal degradation, discarding the incomplete transcript. **C**, RNAPII can bypass certain lesions, but this may result in transcriptional mutagenesis. **D**, Displacement of the RNAPII to access the lesion for repair by reverse translocation with transcription factor IIS (TFIIS)—stimulated partial degradation of the nascent transcript. **E**, Initiation of the repair process by remodeling of RNAPII without displacing it. This would allow nicking of the DNA strand by the xeroderma pigmentosum group G (XPG) protein.

to have decreased synchrony and reduced synapse density.¹⁶ Moreover, mitochondrial dysfunction has been reported in CSA and CSB cells.^{17,18}

Epidemiology. CS is an extremely rare autosomal recessive disorder. In 1936, Sir Edward A. Cockayne first described the disease in 2 patients who had cachectic dwarfism with retinal atrophy and deafness.¹⁹ Kleijer et al²⁰ estimated that the minimum

incidence in Western European countries (ie, France, Italy, the United Kingdom, and the Netherlands) was 2.7 per million live births in the overall population; the incidence among indigenous Europeans was estimated to be 1.8 per million live births. There have been some reports that it is more prevalent in some countries such as Canada,²¹ Japan, and some middle Eastern and Western Asian countries.²⁰ Information on other parts of the world has been limited but it is believed to be similar to the incidence in Europe.²² However, it has been suggested that with the increasing availability of diagnostic tests, a higher incidence could be related to previously underdiagnosed cases.²³

Clinical features. Patients with CS present with 3 major characteristic manifestations: microcephaly, stunted growth, and progressive neurologic dysfunction caused by leukodystrophy (ie, progressive degeneration of the white matter; Fig 2). In addition, 3 of 5 of the following minor criteria have been recommended for a positive diagnosis: ultraviolet B light and visible light photosensitivity, dental caries, pigmentary retinopathy or cataracts, sensorineural hearing loss, and cachectic dwarfism with stooped posture.²⁴ These are usually accompanied by numerous additional abnormalities, including gait defects, contractures, spasticity, tremors, demyelination of the peripheral nerves, basal ganglia calcifications, progeria with shortened lifespan, hypertension, and osteoporosis. Aside from photosensitivity, other skin manifestations include dry, thin skin, dry hair, and anhidrosis. Frouin et al²⁵ recently reported an acral cyanotic livedo and edema of the extremities in 75% of their patients. It is important to note that unlike XP, patients with CS do not develop sun-induced pigmentation or ultraviolet light-related skin malignancies despite their photosensitivity. In addition, there have been no reports of cancers in any of the nearly 1000 patients diagnosed with CS to date.²⁶ Other rarer dermatologic findings include nail dystrophies and exaggerated hair loss.

Accelerated aging changes seen in patients with CS resembled normal chronologic aging features, albeit occurring at a younger age. These features include the loss of subcutaneous fat, a decline in hearing, cognition, and renal function, cardiovascular changes, such as atherosclerosis, arteriolosclerosis, and chronic hypertension, and endocrine abnormalities, such as diabetes.²⁷

Given this variation of phenotypes in patients with CS, CS has been classified, based on a publication by Nance and Berry,²⁴ into 3 groups based on age of onset: type I classic CS, type II early onset CS, and type III mild or atypical CS. The

Table II. Factors required for transcription-coupled repair but not for global genomic repair

Protein	Role	Comments	Diseases
CSA (ERCC8)	Ubiquitin ligase complex	WD repeats	CS and UV ^S S
CSB (ERCC6)	Chromatin remodeling and transcription elongation	RNAPI cofactor	CS, UV ^S S, COFS syndrome, and DSC syndrome
XAB2	Transcription factor	Link between XPA and RNAPII	Unknown
UVSSA	Link RNAPII-USP7	—	UV ^S S
USP7	Deubiquitylation	—	Unknown
TFIIS	RNAPII elongation	Stimulation of transcript cleavage by RNAPII	Unknown
HMGN1	Chromatin relaxation	—	Unknown
p300	Chromatin remodeling	—	Unknown
SPT16	Chromatin remodeling	Subunit of the FACT complex	Unknown
—	RNA biogenesis	THO, TREX, and THSC/TREX-2 complexes	Unknown
hOGG1	Glycosylase	Recognition of 8-oxoguanine	Unknown

COFS, Cerebro-oculo-facio-skeletal; CS, Cockayne syndrome; DSC, De Sanctis–Cacchione; ERCC, excision repair cross-complementing group; FACT, facilitates chromatin transcription; THO, nuclear protein complex required for transcription elongation; THSC, multifunctional protein complex involved in RNA export through the nuclear pore complex; TREX, transcription/export; UVSSA, UV-stimulated scaffold protein A; UV^SS, UV-sensitivity syndrome; WD, tryptophan-aspartate.



Fig 2. A child with Cockayne syndrome. Note the microcephaly and typical Cockayne syndrome facial features, such as crowded facial features and sunken eyes with a loss of orbital fat. (Reprinted, with permission, from: Paller, A and Mancini, A. *Hurwitz Clinical Pediatric Dermatology: A Textbook of Skin Disorders of Childhood and Adolescence*. 5th Ed. Elsevier Health Sciences, 2015.)

severity of the condition and life expectancy of patients has been observed to correlate with the age of onset.²³ Type I CS represents the classical moderate subtype, in which patients develop their first

symptoms during their first 2 years of life and fulfill the diagnostic criteria during childhood, with a mean age of death at 16 years of age.²⁴ Type II early onset CS represents the severe subtype with clinical manifestations at birth and diagnostic criteria fulfilled during infancy, with a mean age of death at 5 to 6 years of age.²⁴ Type III CS is a late onset subtype that is milder, with the first symptoms appearing at 3 to 4 years of age and diagnostic criteria fulfilled in the early teens, with a mean age of death at 30 years. Natale²² has described the naming of this traditional classification to be confusing and proposed a formal renaming of these groups according to their clinical severity: mild CS (type III), moderate CS (type I), and severe CS (type II). However, Laugel²³ suggested that CS is a condition with a continuous spectrum of disease presentations and severity and emphasized that this is important to keep in mind. Laugel²³ proposed modifications to the above mentioned clinical diagnostic criteria by Nance and Berry²⁴ to improve specificity and sensitivity to 98% and 90%, respectively, with a 97% in both negative and positive predictive values. The modified criteria would include developmental delay, progressive growth failure, and progressive microcephaly as the major criteria, and enamel hypoplasia and bilateral, progressive enophthalmia to replace dental caries and cachectic dwarfism in the minor criteria.

Management. There is no cure for CS. Treatment of the condition is largely symptomatic and supportive to prevent the progression of clinical symptoms. Sun avoidance and photoprotection are important and are discussed below.

Aside from the management of cutaneous photosensitivity, management of complications in

various systemic organs (eg, musculoskeletal, developmental delay, vision, hearing, cardiovascular, and renal) are equally important to prevent further progression and to ensure a good quality of life. Given the different organs involved, patients should be primarily managed by a pediatrician with referrals to relevant clinical specialties when necessary.²⁶

Early and regular physiotherapy to prevent limb contractures together with physical aids and suitable medications are important in the care of musculoskeletal complications. Similarly, special education and visual and hearing aids will complement the other general management strategies. Some centers have advocated the use of dietary antioxidant supplements, such as vitamins C, E, and catechins, together with early stimulation of the brain and movements to retard the progression of neuromusculoskeletal symptoms.²⁸

Overlap of xeroderma pigmentosum/ Cockayne syndrome

Key points

- Patients with an overlap of xeroderma pigmentosum/Cockayne syndrome have clinical features and biochemical characteristics of both syndromes
- Certain mutations in *XPB*, *XPD*, and *XPG* genes result in xeroderma pigmentosum/Cockayne syndrome phenotypes

Greenhaw et al²⁷ first described 2 siblings who had clinical features of XP but with biochemical characteristics of CS. Patients often have manifestations of cutaneous photosensitivity to ultraviolet B light, developmental delay, mental retardation, neurologic involvement, and cutaneous pigmentation, which are typically present in cases of XP and of CS. However, they tend to have severe neurologic complications with milder cutaneous involvement. *XPB* and *XPD* are essential components of the TFIIH transcription complex, and the *XPG* endonuclease serves as a stabilizer for the complex. Certain mutations in the *XPB*, *XPD*, and *XPG* genes result in XP/CS phenotypes, which may arise from abnormalities in transcription by RNAPII in addition to defective NER (reviewed by Singh et al¹²).

Management of these patients is similar to that described for patients with CS.

Cerebro-oculo-facio-skeletal syndrome

Key points

- Cerebro-oculo-facio-skeletal syndrome is a rare autosomal recessive disorder
- Mutations in *CSB*, *ERCC1*, *XPD*, or *XPG* can cause cerebro-oculo-facio-skeletal syndrome

- Patients with cerebro-oculo-facio-skeletal syndrome have some clinical manifestations typical of patients with Cockayne syndrome, with additional features including severe hypotonia, impaired reflexes, poor vision, and the distinctive facial features of small eyes, low-set ears, microcephaly, and a small jaw

Background. Cerebro oculo-facial-skeletal (COFS) syndrome shares some of the clinical manifestations typical of patients with CS with additional features, such as severe hypotonia, impaired reflexes, poor vision, and distinctive facial features, including small eyes, low-set ears, microcephaly, and a small jaw. The limbs, skull, heart, and kidneys may also be abnormal. Mutations in *CSB*, *ERCC1*, *XPD*, or *XPG* can cause COFS syndrome. The severity of the symptoms leads to lethality during infancy or early childhood; the patients or their cells are usually photosensitive, although the action spectrum is not known.¹³

Epidemiology. COFS syndrome is a rare autosomal recessive disorder that was first reported in 2 siblings within the Manitoba aboriginal population in 1971.²⁹ As of 2008, only 14 cases described to have COFS syndrome had full evaluations at the clinical, cellular, and molecular levels, and most cases were described from this aboriginal population.³⁰ The exact epidemiology of COFS syndrome can be difficult to delineate, because clinical features of reported cases often overlap with other autosomal recessive disorders involving the eyes and the brain, such as Warburg micro syndrome or Martsolf syndrome.³⁰

Clinical features. Laugel et al³⁰ have proposed that the diagnostic criteria of COFS syndrome should include congenital microcephaly, congenital cataracts or microphthalmia, arthrogryposis, severe developmental delay and postnatal growth failure, and facial dysmorphism with prominent nasal root or overhanging upper lip and a defect in the TCR pathway. Clinical features of COFS syndrome often overlap with features of the severe subgroup of type II CS, such as multiple spine and joints contractures, congenital cataracts, and microphthalmia²⁹; patients or their cells are usually photosensitive, although the action spectrum is not known.¹³ Various studies have suggested that they could represent disorders of different severity of the same clinical syndrome,³¹⁻³³ but there are important differences. Microphthalmia and arthrogryposis—commonly found in patients with COFS syndrome—are rare in patients with type II CS. Patients with COFS syndrome also usually do not have a cachectic appearance, which is commonly described in patients with type II CS. The mean age of death for patients with COFS syndrome is 3.5 years.³⁰

Management. Treatment of COFS syndrome is largely symptomatic and supportive. Aside from the supportive management discussed in the CS section above, patients with COFS syndrome should be followed-up closely for recurrent respiratory infections. They also often require assisted or tube feeding.

Ultraviolet-sensitive syndrome

Key points

- Ultraviolet-sensitive syndrome is comprised of 3 complementation groups with mutations in the *CSA*, *CSB*, or *UVSSA* genes
- Ultraviolet-sensitive syndrome cells are defective in transcription coupled repair but have normal global genomic repair
- Patients have cutaneous pigmentation in sun-exposed areas but do not have an increased risk of cutaneous malignancies

Ultraviolet-sensitive syndrome (UV^SS) was first described by Itoh et al.³⁴ Individuals with UV^SS are photosensitive and present with acute sunburn, dryness, freckling, pigmentation anomalies, and telangiectasias in sun-exposed areas of the skin; however, just as with patients with CS, no tumors have yet been reported in their skin or internal organs. The action spectrum of photosensitivity is not known. In striking contrast with CS and other DNA repair-deficiency disorders, no pathologies other than sunburn and freckles have been associated with UV^SS. Although it is likely that there are hundreds or thousands of people with UV^SS worldwide, their clinical features are so mild that they may easily elude diagnosis as being affected by a genetic disease.

To date, 8 patients have been characterized with UV^SS; 6 are Japanese and 2 are white. There are 3 complementation groups of UV^SS, with mutations in the *CSA*, *CSB*, or *UVSSA* genes. Like CS cells, UV^SS cells are defective in TCR but have normal global genomic repair.¹⁰ Both cellular types are hypersensitive to damaging agents that cause bulky adducts; in contrast to CS cells, UV^SS cells show normal resistance to oxidizing chemicals.^{17,35} As mentioned above, several lines of evidence point to defects in mitochondrial metabolism as the underlying cause of the neurologic and growth defects in patients with CS; consistent with the lack of hypersensitivity to oxidation, UV^SS cells have normal mitochondrial function.^{17,18}

The management of patients with UV^SS is largely focused on the prevention of cutaneous complications, such as photosensitivity and cutaneous pigmentation. Unlike the other conditions discussed in this article, no other organ systems are involved.

Trichothiodystrophy

Key points

- Trichothiodystrophy is a heterogeneous autosomal recessive disorder
- It mainly affects neuroectodermal-derived tissues, but there can be multisystem involvement
- Trichothiodystrophy is comprised of 6 complementation groups, but only 3 involve photosensitivity, with mutations in the *XPB* (*ERCC3*), *XPD* (*ERCC2*), and *TTDA* genes
- Cutaneous manifestations include photosensitivity, ichthyosis, brittle hair, and nails
- One distinctive diagnostic feature is a tiger tail-like pattern of the hair under polarized light
- Other extracutaneous manifestations include intellectual impairment, decreased fertility, short stature, microcephaly, osteoporosis, premature aging, proneness to infections, dental caries, hearing loss, and cataracts

Background. Trichothiodystrophy (TTD) is comprised of 6 complementation groups, of which only 3 are associated with photosensitivity and are the result of mutations in genes involved in the NER pathway, namely *XPB* (*ERCC3*), *XPD* (*ERCC2*), and trichothiodystrophy type A (*TTDA*); the proteins encoded by these genes are subunits of the transcription/DNA repair factor TFIIH. Unlike the syndromes described above, photosensitive TTD patients are defective in both the global and the transcription-coupled subpathways of NER; however, in contrast to NER-deficient XP, these defects do not result in a heightened incidence of cancer. As mentioned above, some mutations in *XPD* result in combined XP/TTD phenotypes. Reduced concentrations, increased instability, and abnormal function of TFIIH have been reported in all TTD patients tested, suggesting that this may be a “transcription disease” caused by abnormal architecture of the complex; in contrast, mutations in *XPD* and *XPB* genes in patients with XP affect the adenosine triphosphatase or helicase activities of TFIIH that are specifically necessary for NER without affecting transcription.⁸ Mutations in the gene coding for M-phase-specific PLK1-interacting protein, *MPLKIP* (*TTDN1*), are responsible for one of the nonphotosensitive forms, BIDS (ie, brittle hair, intellectual impairment, decreased fertility, and short stature); the genetic bases for the other 2 nonphotosensitive complementation groups have not yet been identified.³⁶

Epidemiology. TTD is a heterogeneous autosomal recessive disorder that, although mainly

affecting neuroectodermal-derived tissues, can have multisystem involvement. It was first described in 1968 by Pollitt et al³⁷ in a pair of siblings; Price et al³⁸ subsequently coined the term “trichothiodystrophy” to describe this condition in 1980. In a large review of TTD in 2009, 122 cases were described and characterized.³⁹ Kleijer et al²⁰ estimated that the minimum incidence of TTD in Western European countries (ie, France, Italy, the United Kingdom, and the Netherlands) was 1.2 per million live births in the overall population; the incidence among indigenous Europeans was estimated to be 1.1 per million live births.

Clinical features. Patients with TTD present with intellectual impairment and other features shared with patients with CS. However, the most notable feature of TTD is the presence of brittle hair and nails; the tiger tail–like pattern of the hair under polarized light is a unique and distinctive diagnostic feature (Figs 3 to 5). Hair shaft abnormalities caused by reduced sulfur content include trichoschisis, trichorrhexis nodosa, and ribbonning.⁴⁰ The acronyms PIBIDS, IBIDS, BIDS, and PBIDS have been used to classify patients according to their individual set of symptoms: *photosensitivity, ichthyosis, brittle hair, intellectual impairment, decreased fertility, and short stature*; patients may also exhibit microcephaly, osteoporosis, skeletal abnormalities, nail abnormalities, premature aging, proneness to infections, dental caries, hearing loss, and cataracts. A shortened lifespan has been reported.⁴¹

Other cutaneous manifestations were mainly ichthyosis described to have features of the vulgaris type with small, white scale on the legs. An aspect of collision baby at birth was observed in nearly one-third of the patients.³⁹

Management. In addition to the need for rigorous photoprotection strategies, regular emollients are encouraged in view of the ichthyosis commonly present in patients with TTD. Supportive care strategies for brittle hair and dystrophic nails are also important.

Beyond cutaneous manifestations and neurodevelopmental complications, physicians should also be cognizant of the increased risks of recurrent infection and dental caries among patients with TTD.

Photoprotection

Key points

- Rigorous photoprotection is required, especially in photosensitive hereditary skin disorders
- Photoprotection consists of seeking shade when outdoors, wearing sun-protective



Fig 3. A child with trichothiodystrophy. Note the sparse, brittle hair. (Photograph courtesy of Tor A. Shwayder, MD, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.)



Fig 4. Trichoschisis—a clean break in the hair shaft on hair microscopy—is a typical finding in patients with trichothiodystrophy. (Photograph courtesy of Tor A. Shwayder, MD, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.)

clothing, a wide brimmed hat, and sunglasses, and applying broad-spectrum sunscreens with a sun protection factor of >30

- **Patients who practice rigorous photoprotection may be at risk for vitamin D deficiency; therefore, oral vitamin D supplementation should be recommended**

Photoprotection is an important part of the management of DNA repair-deficiency photodermatoses and is similar to that advised for other photodermatoses.⁴² The major difference is the rigorousness of photoprotection, especially in the cancer-prone DNA repair-deficiency disorders



Fig 5. The tiger tail-like pattern of hair viewed under polarized light microscopy. This is a distinctive diagnostic feature of patients with trichothiodystrophy. (Photograph courtesy of Tor A. Shwayder, MD, Department of Dermatology, Henry Ford Hospital, Detroit, Michigan.)

covered in the first article in this series, such as XP.⁴³ Photoprotection consists of seeking shade when outdoors, wearing sun-protective clothing, a wide-brimmed hat, and sunglasses, and applying broad-spectrum sunscreens with a sun protection factor of >30.⁴⁴⁻⁴⁶ Sunscreens should be used daily and should be applied to all areas of exposed skin in the morning, with reapplication every 2 to 3 hours when outdoors. It should be noted, however, that UV protection does not prevent the neurodegeneration associated with some of these disorders.^{47,48}

The goal of photoprotection is to significantly reduce the amount of UV radiation reaching the skin of these patients. For most of these disorders, careful studies on the degree of photosensitivity and the action spectrum have not been performed.⁴³ Tamura et al⁴³ reported the concept of photoprotection of patients with XP as surrounding them in layers of protection: an outer layer of environmental modification, a middle layer of photoprotective clothing, and an innermost layer of sunscreens or physical blocking lotions/creams on the skin. Environmental modifications include surveying the outdoor environment with UV meters, timing and restriction of outdoor activities, using UV-blocking window films, and indoor incandescent lighting. These patients are at risk for vitamin D deficiency⁴⁹; therefore, serum vitamin D levels should be monitored and oral vitamin D supplementation given if necessary.⁴³

In conclusion, photosensitive hereditary skin disorders with defects in the TCR pathway and normal global genomic NER belong to a group of photodermatoses with varying skin manifestations but not cutaneous malignancies. Diseases such as CS, COFS syndrome, and TTD have significant musculoskeletal and neurodevelopmental defects along

with premature aging features and comparatively mild cutaneous manifestations. On the other hand, patients with UV^SS present only with sunburns and freckles and no systemic complications. Photosensitivity is a consistent feature in all of these diseases; these patients require vigorous photoprotection measures. However, it should be noted that photoprotection does not retard the development of noncutaneous systemic complications. Therefore, a multidisciplinary supportive approach is crucial in the management of these patients.

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Primary cicatricial alopecia



Lymphocytic primary cicatricial alopecias, including chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham-Little syndrome

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Learning objectives

After completing this learning activity, participants should be able to identify the individual characteristics of each form of scarring alopecias and possible coexisting extracranial features.

Disclosures

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Both primary and secondary forms of cicatricial alopecia have been described. The hair follicles are the specific target of inflammation in primary cicatricial alopecias. Hair follicles are destroyed randomly with surrounding structures in secondary cicatricial alopecia. This 2-part continuing medical education article will review primary cicatricial alopecias according to the working classification suggested by the North American Hair Research Society. In this classification, the different entities are classified into 3 different groups according to their prominent inflammatory infiltrate (ie, lymphocytic, neutrophilic, and mixed). Part I discusses the following lymphocytic primary cicatricial alopecias: chronic cutaneous lupus erythematosus, lichen planopilaris, frontal fibrosing alopecia, and Graham–Little syndrome. (J Am Acad Dermatol 2016;75:1081–99.)

Key words: alopecia; cicatricial; fibrosis; follicles; hair; hair loss; lymphocytes; neutrophils; permanent.

INTRODUCTION AND GENERAL ASSESSMENT

Key points

- Hair loss may progress subclinically
- Diagnosis is often delayed
- All hair-bearing areas should be examined

- Perifollicular accentuation and isolated hairs are precious clues
- Unless there is a true primary infection, cultures are usually negative in patients with primary cicatricial alopecia
- Laboratory testing should be performed in accordance with the clinical setting

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Abbreviations used:

CCLE:	chronic cutaneous lupus erythematosus
DIF:	direct immunofluorescence
DLE:	discoid lupus erythematosus
FFA:	frontal fibrosing alopecia
ITA:	intralesional triamcinolone acetonide
LE:	lupus erythematosus
LPP:	lichen planopilaris
MMF:	mycophenolate mofetil
NAHRS:	North American Hair Research Society
PDIRS:	premature desquamation of the inner root sheath

Primary cicatricial alopecias (PCAs) represent a group of poorly understood conditions in which the destruction of follicular structures leads to permanent hair loss. Although some familial cases have been described, most cases of PCA are acquired. A working classification for PCA was proposed by the North American Hair Research Society¹ (**Tables I and II**). This classification may evolve as more data become available. PCAs account for approximately 5% of cases in specialized hair clinics,²⁻⁴ and the ratio of lymphocytic to neutrophilic or mixed PCA is 4:1.^{2,3}

Hair loss may progress subclinically,⁵ and scalp biopsy specimens obtained from clinically “normal” areas may have evidence of disease.^{6,7} A significant amount of hair is usually lost before the alopecia is apparent, making it difficult to precisely determine its onset.^{8,9} Patients are often aware of their alopecia for >1 year before consulting a dermatologist.^{10,11} Inflammation frequently extends well beyond the alopecic area(s). Assessment is done by parting the hair over the entire scalp and looking for signs of alopecia and inflammation. Hair-bearing areas, the skin, mucosa, and the nails should be examined (**Table III**). Subtle clues to PCA may be easily overlooked. Discrete, millimeter-wide alopecic patches and perifollicular accentuation may be the only signs present. Patients may present without obvious areas of hair loss but rather diffuse hair thinning and discrete perifollicular erythema and scaling. They are often misdiagnosed with pattern hair loss and seborrheic dermatitis (**Fig 1**). Long-standing plaques without a history of regrowth and the presence of isolated hair(s) (**Fig 2**) within the plaques should raise suspicion for PCA. Female pattern hair loss (FPHL) or male pattern hair loss (MPHL) may be present concomitantly. The pull test (**Table IV**) is a good indicator of hair loss activity. Even though ≤10% of hairs are in the telogen phase, not all of them are ready to shed at the same time (the telogen phase lasts 2-4 months). In our experience, pulling 50 to 100 hairs (in 7-10 pulls) in a normal individual will usually yield few telogen hairs

(approximately 2-5 hairs).¹² One or more hair(s) coming out at each pull is considered positive. A false-positive pull test occurs if the hair is not washed for several days. Active hair shedding usually yields a positive pull test even if the hair was washed and groomed shortly before examination. One should assess the surface area (**Table IV**) affected by hair loss and the surface area affected with inflammation.^{13,14} Serial photographs may not detect slowly evolving hair loss, but a baseline photograph is useful for long-term follow-up. Taking and classifying photographs can be time consuming. An alternate option is to use the patient’s smartphone or other mobile device to take pictures that can then be used during subsequent visits. Dermoscopy can help differentiate non-cicatricial alopecia from cicatrical alopecia and can improve biopsy site selection^{4,15-25} (**Table V**). A scalp biopsy specimen²⁶⁻²⁸ (**Table IV**) helps confirm the diagnosis in clinically ambiguous cases and identifies the nature and density of the inflammatory infiltrate. One biopsy specimen usually suffices, and it should be processed with horizontal, transverse sections rather than vertical sections.^{3,28,29} In cases of lupus erythematosus (LE), a second biopsy specimen should be obtained; 1 half is used for direct immunofluorescence (DIF) study and the other is processed with vertical sections. Fungal and bacterial cultures should be performed when there is suspicion of tinea capitis or bacterial infection and to guide the choice of antibiotic, but most cultures are negative or lead to nonspecific pathogens.³⁰⁻⁴¹ Many series and case reports have reported normal or nonspecific laboratory tests, including complete blood cell count, thyroid function tests, iron, zinc, ferritin levels, and many others.^{1,9,10,30,34,36,38-40,42-62} A recent study reported a higher prevalence of hypothyroidism in 355 patients with frontal fibrosing alopecia (FFA; 15%) compared to the general population (4%).⁶² Although some biochemical or nutritional anomalies have been inconsistently reported,⁵⁰ there is no blood test specifically recommended for PCA. Laboratory studies should be dictated by the clinical context and to monitor potential side effects of treatment. Antinuclear antibody levels should be assessed in patients with LE. Syphilis should be ruled out if suspected.⁶³ Low ferritin levels have been a cause for debate.⁶⁴ It is controversial to treat iron deficiency without anemia, and there is no clear proof that it reduces hair loss.^{50,65-67}

GENERAL MANAGEMENT OF PRIMARY CICATRICIAL ALOPECIA

Key points

- Evidence supporting therapy is generally poor

- **The aims of treatment are to stop or reduce hair loss, control the symptoms, and reduce the clinical signs of inflammation.**
- **Regrowth should not be expected**
- **Choice of therapy is guided by the type of inflammatory infiltrate**
- **Duration of therapy is guided by the response and relapse rate**
- **No evidence supports the use of most over the counter products and shampoos**
- **Potent corticosteroids and intralesional triamcinolone acetonide are commonly used in all forms of primary cicatricial alopecia**
- **Minoxidil helps maximize hair growth of the remaining follicles**
- **Camouflage techniques should be provided**
- **Actinic keratosis and squamous cell carcinoma should be suspected in nonresponsive lesions**

The evidence supporting any treatment for PCA is generally poor and consists mostly of retrospective case reports, small series, and expert opinion (level of evidence, III and IV). It is difficult to get a good sense of the true efficacy of any given treatment because little is known about the natural evolution of PCA or what represents a good clinical response. Methods of assessment used, such as photographs, hair count, or scoring systems, often differ and do not always yield comparable data. Despite their flaws, these reports can give clinicians some direction in how to manage their patients. In our experience, many patients tend to remain stable over the years, as confirmed with baseline photographs.

The aims of treatment are to stop or reduce hair loss, control the symptoms (ie, itching, burning, and tenderness), and reduce the clinical signs of inflammation. In our experience, it is difficult to completely eliminate inflammation. These goals must be discussed with patients so that expectations are realistic. Although some regrowth occasionally occurs, it is uncommon and is not the aim of treatment. Therapy should be applied to active hair-bearing areas. Duration of treatment should be guided by clinical response and relapse rates. It should be emphasized to patients that PCA is not their doing; it is neither contagious nor caused by unclean hair salon equipment. Actinic keratoses and squamous cell carcinomas have been reported in patients with PCA, especially LE. Localized or isolated lesions that fail to respond to treatment should raise suspicion (Fig 3).⁶⁸⁻⁸¹

Considerable anxiety is associated with alopecia.⁸²⁻⁸⁴ Support groups are helpful and consultation with a psychologist is sometimes advisable.

Patients can be directed to the North American Hair Research Society (www.nahrs.org) and Cicatricial Alopecia Research Foundation (www.carfint.org) websites for more information on PCA. When camouflage is necessary, options should be provided (Table VI). Initially, most patients are reluctant to use hairpieces, but they can enhance self-confidence and quality of life. If possible, suggestions as to where patients can buy natural-appearing wigs are often appreciated.

Physicians' experience treating these patients varies, as do treatment plans. Specific management will be discussed with each entity, but general management tips will first be discussed. Over the counter products for hair loss are plentiful and patients frequently use them, sometimes spending thousands of dollars on these products. However, data on their safety and efficacy are lacking. The absence of legislation does not allow governmental control of the purity or consistency of these products, and their advertised results are often unrealistic.^{85,86} We usually discourage their use. Patients can use any shampoo; there is no need to buy expensive salon-based shampoos. Patients with hair loss may fear washing their hair, but frequency of shampooing does not make a difference in the total number of hairs lost. However, fewer hairs are found in the drain with frequent washes, and counts are more numerous with infrequent washes. This should be explained to the patient. Hair counts are discouraged. There is no firm evidence that chemical treatments (eg, coloring or perming) are damaging to patients with PCA (Table VII).

Potent topical corticosteroids and topical tacrolimus are commonly used for all PCAs and are often considered first-line treatments.^{2,11,50,62,87-96} They help relieve symptoms of itching and burning and reduce inflammation. Various formulations are available (ie, ointment, lotion, solution, or foam). Fluocinolone acetonide in oil (Derma-Smooth; FS Hill Dermaceuticals, Sanford, FL) or the combination of calcipotriol and bethametasone (Dovobet; Leo Pharma, Parsippany, NJ) are especially useful when scaling is significant.⁹³

Tacrolimus is useful when the use of corticosteroids cannot be sufficiently reduced. It can be compounded at 0.1% to 0.3% in Cetaphil lotion (Galderma, Fort Worth, TX).⁹⁷ Topical treatments are used up to twice daily, initially for 4 to 12 weeks, and then tapered. There is no evidence that long-term maintenance treatment with applications 2 to 3 times per week is helpful, but there is no real disadvantage and it may slow progression or delay relapses.^{94,96} Intralesional triamcinolone acetonide (ITA) injections are helpful, especially in

Table I. North American Hair Research Society working classification

Lymphocytic	
Chronic cutaneous lupus erythematosus	
Lichen planopilaris	
Classic lichen planopilaris	
Frontal fibrosing alopecia	
Graham–Little syndrome	
Classic pseudopelade (Brocq)	
Central centrifugal cicatricial alopecia	
Alopecia mucinosa	
Keratosis follicularis spinulosa decalvans	
Neutrophilic	
Folliculitis decalvans	
Dissecting cellulitis/folliculitis	
Mixed	
Folliculitis (acne) keloidalis	
Folliculitis (acne) necrotica	
Erosive pustular dermatosis	
Nonspecific	
Defined as an idiopathic scarring alopecia with inconclusive clinical and histopathologic findings. May include the end stage of a variety of inflammatory cicatricial alopecias	

symptomatic or active patients who have had a positive pull test.^{2,10,29,62,98} They are administered every 4 to 6 weeks on affected hair-bearing areas at concentrations ranging from 2.5 to 10 mg/mL.^{91,92} Injections are made approximately 1 cm apart, and ≤ 0.1 mL is injected per injection site. Diluting with injectable normal saline and using a 30-gauge syringe reduce pain. Inflammation is mostly localized within the dermis, but no study has confirmed the superiority of intradermal over subcutaneous injections. Subcutaneous injections are less painful and reduce the risk of atrophy. Some patients are more prone to atrophy, but it is reversible. Avoiding areas of denting and lowering the concentration of ITA in subsequent treatments usually suffice. Lower concentrations should be used near the face. When the patient's condition is stable, tapering is done by gradually increasing the interval between injections up to 12 weeks and then discontinuing it.

Minoxidil solution will not control PCA, but it may help maximize hair growth. If minoxidil cannot be used two times per day, once-daily application is acceptable.^{29,44,62,63,99} Both minoxidil 2% and 5% can be used, although 2% may be better tolerated.¹⁰⁰ No study has compared the efficacy of minoxidil 2% versus 5% in patients with cicatricial alopecia. One study found that both were similarly effective for the treatment of FPHL, with a trend toward better efficacy of minoxidil 5%.¹⁰⁰ There are

Table II. Synonymous or conditions included in the description

Graham–Little syndrome		Graham Little–Piccardi-Lassueur syndrome
Central centrifugal cicatricial alopecia		Central elliptical pseudopelade in whites
		Follicular degeneration syndrome
		Hot comb alopecia
		Pseudopelade in African Americans
Keratosis follicularis spinulosa decalvans		Keratosis follicularis spinulosa
Dissecting cellulitis		Dissecting folliculitis
		Dissecting perifolliculitis
		Hoffman disease
		Perifolliculitis capitis
		Perifolliculitis capitis abscessens et suffodiens
Folliculitis (acne) keloidalis		Acne keloidalis nuchae
		Dermatitis papillaris capillitii
		Folliculitis nuchae scleroticans
		Folliculitis keloidalis chronica nuchae
		Keloidal folliculitis
		Lichen keloidalis nuchae
		Syphosis nuchae
		Syphosis framboesiformis
Folliculitis (acne) necrotica		Acne necrotica varioliformis
		Acne necrotica

Table III. Cutaneous findings related to specific primary cicatricial alopecias

Chronic cutaneous LE	Cutaneous LE lesions, nonspecific LE-associated lesions, such as leukocytoclastic vasculitis, livedo reticularis, noncicatricial alopecias, Raynaud phenomenon, lupus pernio, and periungual or nail changes
Lichen planopilaris	Lichen planus lesions on skin, mucosa, and nails
Frontal fibrosing alopecia	Loss of eyebrows, often without inflammation, and lichen planus lesions on skin, mucosa, and nails
Graham–Little syndrome	Nonscarring alopecia of axillae and pubis; follicular papules on the trunk and extremities
Keratosis follicularis spinulosa decalvans	Alopecia in axillae
Dissecting cellulitis	Acne conglobata; hidradenitis suppurativa; arthritis

LE, Lupus erythematosus.



Fig 1. Lichen planopilaris and pattern hair loss. **A**, From a distance, the diffuse hair density and relative preservation of the hairline point to female pattern hair loss. **B**, On careful examination, one notices discrete alopecic areas and perifollicular accentuation pointing to lichen planopilaris. **C**, Lichen planopilaris and male pattern hair loss.



Fig 2. Cicatricial alopecia. Isolated hairs within a long-standing alopecic area are suggestive of cicatricial alopecia.

no good data on the subject of hair transplantation (HT). Even if PCA is controlled for a prolonged period, it may recur at any time. There are reports of PCA developing after HT, but the condition may have been overlooked before the procedure or it may simply have been coincidental. HT in the context of PCA is risky, and we typically do not recommend it. If a patient wants to undergo the procedure, we suggest that they wait until their condition has been under remission for at ≥ 2 years without treatment. Temporary improvement may be achieved, but the long-term benefit cannot be

guaranteed, and significant destruction of grafts has been reported.^{101,102}

LYMPHOCYTIC PRIMARY CICATRICIAL ALOPECIAS

Chronic cutaneous lupus erythematosus

Key points

- Signs and symptoms of systemic lupus erythematosus must be excluded
- Chronic cutaneous lupus erythematosus of the scalp usually responds well to therapy

Chronic cutaneous lupus erythematosus (CCLE) is more common in white and African American women.¹⁰³⁻¹⁰⁵ It may occur at any age, but predominantly occurs between 20 and 40 years of age.¹⁰⁵⁻¹⁰⁷ Solitary or multiple variable size lesions occur primarily on sun-exposed areas and on the scalp^{103,106,108-110} (Fig 4). They consist of well-circumscribed round/oval erythematous, infiltrative scaly plaques. Follicular plugging, telangiectasias, atrophy, and pigment changes are characteristic.^{3,104,111} Changes are seen within the alopecic patch rather than the periphery,¹⁰⁵ and this is useful to differentiate CCLE from lichen planopilaris (LPP). Lesions may be tender or itchy.¹⁰⁵ Most cases are not associated with lesions elsewhere.^{2,104} CCLE can be localized or generalized,^{103,106,108,112,113} and the generalized form is more frequently associated with systemic involvement and laboratory abnormalities.¹⁰³ The presence of nonspecific but LE-related skin lesions (ie, leukocytoclastic vasculitis, thrombophlebitis, livedo reticularis, noncicatricial alopecias, Raynaud phenomenon, lupus pernio, and periungual or nail changes), hematuria, antinuclear antibody titer $>1:320$, and arthralgia are frequently associated with systemic disease.^{103,114} Approximately 5% to 10% of cutaneous LE cases will transition into systemic LE,

Table IV. Methods of assessment

Pull test	Performed by grasping 10-20 hairs between the thumb and index or third finger, close to the scalp, and then pulling along the hair shafts, away from the scalp, slowly but firmly
Obtaining a biopsy specimen of the scalp	Choose active area (inflammation and/or positive pull test) still bearing hairs. Border of an alopecic area is usually favored Trim and clean the area Local anesthesia using xylocaine 1 or 2% with epinephrine (at least 1 mL should be used) Recommended to wait 15-20 min for the epinephrine to be effective and reduce bleeding 4-mm punch is inserted parallel to the direction of emerging hair shaft from the scalp, which is not perpendicular to the scalp in most instances Sample must include subcutaneous fat where anagen follicles are found Suture is recommended to shorten healing time and reduce the risk of bleeding. Using a blue suture makes it easier to remove stitches amongst dark hair
Surface area affected	As a guideline, it is estimated that the scalp is equivalent to 4 times the entire surface of one's palm; 1 palm equals 25% of the scalp while a thumb is equivalent to 1% One could also be inspired by the SALT score used for alopecia areata S0 = no hair loss S1 = <25% hair loss S2 = 25-49% hair loss S3 = 50-74% hair loss S4 = 75-99% hair loss S5 = 100% hair loss

Data from Olsen EA, Hordinsky MK, Price VH, et al. Alopecia areata investigational assessment guidelines—Part II. National Alopecia Areata Foundation. *J Am Acad Dermatol*. 2004;51:440-7.
SALT, Severity of Alopecia Tool.

usually over >5 years.^{115,116} Early hydroxychloroquine treatment is associated with delayed systemic LE onset and with a delay in integument damage development in patients with systemic LE.^{117,118} Some cases may mimic pseudopelade but have the

Table V. Dermoscopic features

Alopecia type	Dermoscopic features
Cicatricial	
LPP	Peripilar white/silver scales Peripilar erythema Keratotic plugs Elongated, concentric blood vessels Violaceous-blue interfollicular areas Big irregular white dots Peripilar white scales Peripilar erythema
FFA	Predominance of follicular ostia Background ivory-white Lack of follicular ostia Eyebrows show regularly distributed red or grey dots Peripilar white scales Peripilar erythema Keratotic plug
DLE	Large yellow dots (keratotic material) Thick arborizing vessels Scattered dark-brown discoloration Follicular red dots
CCCA	1 or 2 hairs emerging together Peripilar white grey halo
CPPB	Lack of follicular ostia Loss of follicular ostia Ivory-white areas Solitary dystrophic hairs White dots
FD	Numerous hairs emerging from the same ostium Peripilar white yellowish scales Peripilar hyperplasia White and milky-red areas Lack of follicular ostia Yellow structureless areas Yellow dots (keratotic material) Dystrophic hair shafts Black dots Pinpoint-like vessels with whitish halo Confluent ivory-white areas Lack of follicular ostia
DC	
Noncicatricial	
Pattern hair loss	Yellow dots (sebaceous, not keratotic) Hair shaft thickness heterogeneity and presence of vellus hairs
Alopecia areata	Exclamation mark hairs Black dots Yellow dots
Telogen effluvium	No specific findings

CCCA, Central Centrifugal Cicatricial Alopecia; CPPB, classic pseudopelade of Brocq; DC, dissecting cellulitis; DLE, discoid lupus erythematosus; FD, folliculitis decalvans; FFA, frontal fibrosing alopecia; LPP, lichen planopilaris.



Fig 3. Actinic keratosis/squamous cell carcinoma should be suspected in the presence of a specific area that fails to respond to treatment.

Table VI. Camouflage

Hairstyle	Hairdressers can suggest styles that cover bare areas
Light hair color	Reduces contrast between hair and visible scalp
Make-up matching one's hair color (eg, crayons, powder)	Reduces contrast between hair and visible scalp
Artificial hair fiber enhancer matching one's hair color	Artificially and temporarily increase hair fiber density
Shampoos, mousses, and fixatives specifically designed to increase hair volume	Increase hair volume
Hats and scarves	Cover bare areas
Hair weaves/hair extension	Increase hair volume and cover bare areas; caution not to add traction
Scalp micropigmentation/tattoo	Covers bare areas/reduce contrast between hair and visible scalp
Hairpieces and volumizers	Cover bare areas; both natural and synthetic fibers are available. Hairpieces should be easy to remove to facilitate treatment application

immunohistopathologic findings of CCLE.¹⁰⁴ Antinuclear antibody titers are positive in 15% to 45% of cases and lupus band test positive in 60% to 80% of cases.^{2,104} The differential diagnosis includes folliculitis decalvans, psoriasis, tinea capitis, and other lymphocytic PCAs.

Histologically, CCLE shows vacuolar interface change with apoptotic keratinocytes along the follicular basal layer (at the infundibulum more often than the isthmus) and sometimes at the dermoepidermal junction between follicles (Fig 5).^{28,105,107,111,119} There is a variably dense lymphoplasmacytic infiltrate that

Table VII. Chemical treatment recommendations

Recommendations

- Avoid excessive heat and chemical treatments
- Hardening gels and sprays may increase hair fragility
- Avoid sewn or glued-in hair weaves and tight braiding that can cause traction and limit treatment application
- When chemical treatments cannot be discontinued
 - Treatment should be applied by a professional
 - Protect the scalp with the application of a petrolatum base
 - Avoid application <1 cm to the scalp
 - Use of a milder formulation
 - Minimize application time (<20 mins)
 - Reduce frequency of treatments to a minimum
 - Alternate with loose braids, wigs, or natural style when possible
 - Avoid concomitant or sequential coloring when relaxers are used

involves the superficial and reticular dermis surrounding blood vessels and adnexae. Sebaceous glands diminish in number. Foci of dense, deep inflammation are sometimes seen, and portions of the fat may be replaced by connective tissue. Other features that are variably present include deep dermal mucin, infundibular hyperkeratosis with ostial plugging, epidermal changes typical of LE, such as parakeratosis, thinning, and thickening of the periodic acid-Schiff-positive basement membrane zone. Widespread loss of elastic fibers in the peri- and interfollicular areas by Verhoeff-van Gieson staining has been described.¹²⁰ DIF testing may show immunoglobulin G (IgG) and C3 along the dermoepidermal junction in both cutaneous and follicular epithelia.^{28,104,121} LPP differs from CCLE by the presence of follicular hypergranulosis, more frequent colloid bodies, and the absence of deep dermal mucin and deep perivascular inflammation. LPP can also feature cytoid body staining with anti-IgM and anti-IgA and patchy or linear fibrinogen deposition along the basement membrane zone in DIF studies.^{122,123}

CCLE of the scalp usually responds well to therapy. Photoprotection (ie, avoidance, sunscreens, and sun protective clothing) is important.¹⁰⁵ Whiting³ suggests that because early lesions are often pruritic, it may be worthwhile to treat these areas with ITA. Topical tacrolimus and pimecrolimus are effective, but potent topical corticosteroids are superior.¹²⁴⁻¹²⁹ Antimalarial drugs are frequently first-line therapy (hydroxychloroquine 200-400 mg daily). A 3- to 6-month trial is necessary. If it fails, quinacrine can be added to enhance efficacy. If no response is seen with the combination after

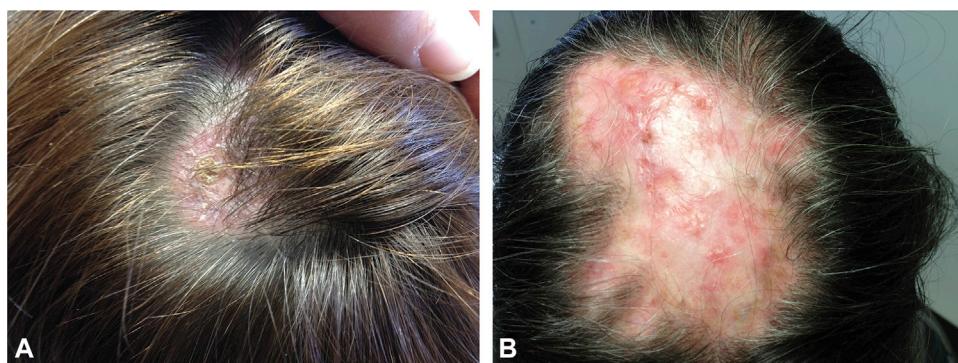


Fig 4. Discoid lupus erythematosus. **A**, A small plaque. **B**, A large plaque.

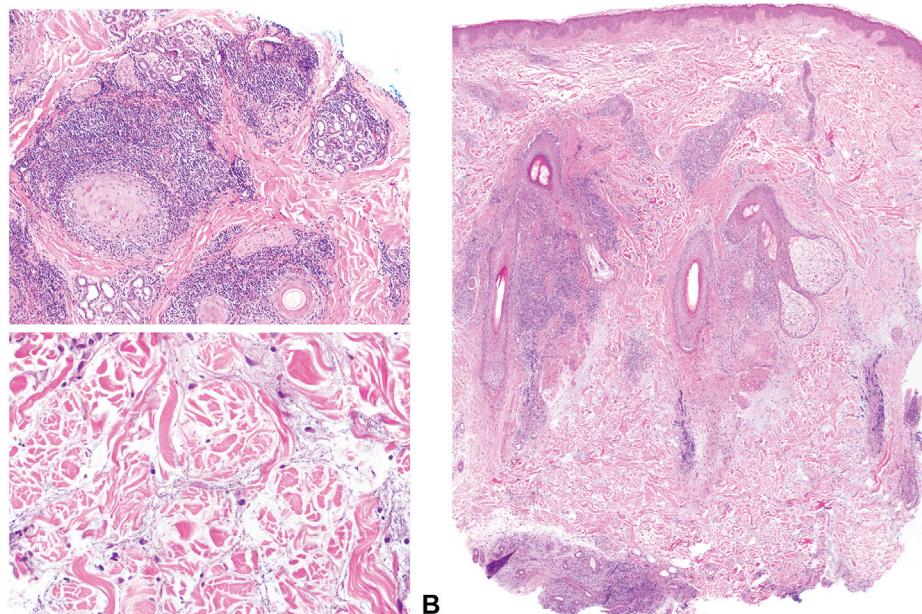


Fig 5. Discoid lupus erythematosus vertical (**A**) and horizontal (**B**) sections featuring prominent perifollicular and perieccrine chronic inflammation, vacuolar interface alteration, and deep mucin deposition (hematoxylin–eosin stain).

3 to 6 months, hydroxychloroquine can be substituted with chloroquine in combination with quinacrine.^{2,3,106,130-144} Approximately 50% of patients with CCLE will respond to hydroxychloroquine, but 20% of patients may become less responsive over a median interval of 2 years despite continued use. Response can be regained with the addition of a second antimalarial drug.¹⁴⁵ Oral corticosteroids—usually prednisone 10-20 mg (≤ 1 mg/kg) daily and tapered over 6 to 8 weeks—are effective.^{2,3,105} We have used daily doses ≤ 40 mg and then tapered.² ITA injections (40-60 mg) may be an alternative to oral prednisone when multiple lesions are present.³ Oral isotretinoin (40-80 mg daily) can be effective. The dose is reduced and eventually stopped when improvement is achieved.^{3,105,146-151} Acitretin (50 mg per day) and hydroxychloroquine showed similar

efficacy in a randomized trial, but adverse events were more frequent and severe with acitretin.¹²⁹ Dapsone (50-100 mg/day) has shown some efficacy in the treatment of CCLE.^{134,152-155} Many authors have reported the efficacy of thalidomide for the treatment of CCLE. Doses of 50 to 100 mg per day are used. A response is usually seen within a few weeks.^{116,134,156-177} Methotrexate can be effective for patients with refractory CCLE.^{3,134,178-189} Azathioprine is used mostly to treat lupus nephritis, but may be effective in difficult cases of CCLE.^{3,134,152,190-193} Cyclosporine is used less commonly, but can be tried in resistant cases.¹⁹⁴⁻¹⁹⁸ Ustekinumab was effective in case reports.^{199,200} Anti-tumor necrosis factor drugs do not appear to be effective and may even induce or exacerbate LE.²⁰¹⁻²⁰⁶ Other treatments reported include



Fig 6. Lichen planopilaris. Shaved hairs allow full evaluation of the extent of lichen planopilaris.

apremilast (20 mg twice daily),²⁰⁷ tocoretinate,²⁰⁸ 1064-nm laser,²⁰⁹ and plasmapheresis.²¹⁰

Lichen planopilaris

Key points

- A partial response to therapy is typical
- Lichen planopilaris can be multifocal, and the entire scalp must be examined

LPP presents with multifocal, coalescing areas of hair loss with mild to moderate perifollicular erythema and scaling (Fig 6).⁹³ Most patients are white women in their early fifties.^{11,211,212} Usually, only the scalp is affected, but LPP may also affect hair on the face^{122,213-218} and body.^{219,220} Cutaneous lichen planus is present in $\leq 50\%$ of patients—depending on the series—but is less common in our experience.^{11,50,122,211} The nails and mucosa are affected in <10% of patients.¹¹ The course of LPP is usually slowly progressive or stable.²²¹

Histologically, LPP features a band-like mononuclear infiltrate obscuring the interface between the follicular epithelium and the dermis (Fig 7).^{28,122,222-226} The epithelial–stromal junction may have prominent vacuoles and dyskeratosis with individually necrotic, polygonal basal keratinocytes. Lymphocytes typically migrate into the outer root sheath. Artifactual clefting between the epithelium and the stroma is common. Colloid bodies are

less common in follicular than in epidermal LP. Inflammation affects the upper portion of the follicle (ie, the infundibulum and isthmus) most severely, but inflammation may extend down the length of the follicle. Occasionally, interfollicular changes of LP are present. Perifollicular fibrosis and chronic inflammation (without interface changes) may be seen in later stages, and the inflammatory infiltrate seems to “back away” from the zone of fibrosis. Premature desquamation of the inner root sheath (PDIRS) is often seen in badly inflamed follicles, but affected follicles can feature normal inner root sheath desquamation. Eventually, sebaceous glands and then follicles are entirely destroyed and replaced by columns of sclerotic collagen (follicular scars). Such scars can be highlighted with elastic tissue stains.¹²⁰ Grouped globular immunofluorescence (usually IgM), especially when found adjacent to the follicular epithelium, is the characteristic pattern seen in LPP.²²⁷ Linear deposits of immunoreactants are typical of lupus. This distinction can be important, because LPP and CCLE may resemble each other both clinically and histologically. LPP does not feature the deep mucin and perivascular and perieccrine dermal lymphocytic infiltrates that are typical of CCLE.

A partial response to therapy is typical. Spontaneous improvement can also occur. Racz et al²²⁸ recently published a review on the treatment of FFA and LPP. A new scoring system to assess response to treatment—the LPP Activity Index—has been proposed.²²⁹ The weight given to symptoms in this score is often not considered in other reports, which focus primarily on disease progression, leading to different efficacy rates.²²⁸ Antimalarial drugs are commonly used to treat LPP. Hydroxychloroquine (6.5 mg/kg/day or 200 mg twice daily) is generally used and is often considered first-line systemic therapy. The largest series are reported by Chiang et al²²⁹ and Spencer et al.²¹² On average, 55% (range, 0-100%) of patients have some improvement; 45% (range, 15-100%) have little or no improvement.^{2,5,50,122,212,221,229,230} Improvement is usually seen within 6 months but is best at 12 months.²²⁹ Some good responders were able to discontinue hydroxychloroquine with no relapse at 1 year.²²⁹ Donati et al⁵ reported decreased hair counts despite improvement of inflammation. Pruritus is often reduced with a negative pull test, but inflammation persists. Improvement was seen in 66% of patients who used acitretin (25 mg per day).²¹² Hair loss as a side effect did not appear to be significant. The largest series using mycophenolate mofetil (MMF; 1000-3000 twice a day) were reported by

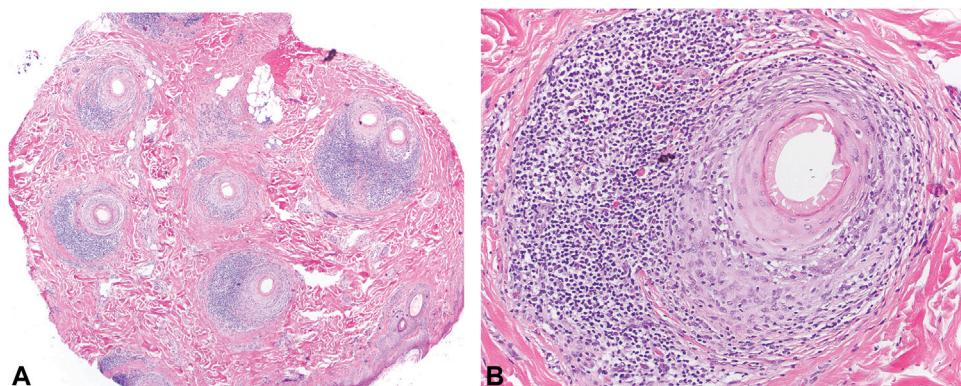


Fig 7. Lichen planopilaris. **A** and **B**, Dense lichenoid chronic inflammation with vacuolar interface alteration, confined to the zone of follicular epithelium (hematoxylin–eosin stain).

Cho et al²¹¹ and Spencer et al.²¹² Most patients failed or had a contraindication to at least hydroxychloroquine and topical treatments. MMF was used for at least 6 months, sometimes up to 4 years, but most patients who responded to MMF did so within the first 6 months.²¹¹ Using MMF (500-1500 mg twice daily), 50% (range, 0-63%) of patients improved while 40% (range, 12-100%) did not respond and 10% of patients discontinued because of adverse events.^{211,212,230-232} Most patients respond to treatment with cyclosporine 3 to 5 mg/kg/day; some patients achieved remission.^{11,122,218,221,231,233} Maximal response was seen within 3 to 5 months. Treatment was discontinued when clinical response was obtained. Mild to moderate growth of tiny textured scalp hairs can be seen but reverses after discontinuing therapy. Most patients seem to recur at some point after discontinuation, but improvement may last a few months and even >1 year.

Pioglitazone (hypoglycemic drug, 15-30 mg per day) has been reported to have some efficacy in LPP.^{230,234,235} The higher dose seems to be more effective.²³⁴ Relapse usually occurs with discontinuation,²³⁵ but some experienced a prolonged remission.²³⁰ There are safety concerns regarding pioglitazone—namely, an increased risk of bladder cancer and heart failure. These adverse events are linked to long-term use (>1 year), cumulative doses, and individual susceptibility.²³⁶⁻²⁵¹

Few reports have discussed the use of thalidomide (100-200 mg/day), and both improvement and failure have been reported.²⁵²⁻²⁵⁴ Methotrexate does not seem to be effective.²¹² Navarini et al²⁵⁵ reported the use of the handheld XTRAC excimer laser (308-nm ultraviolet B light; PhotoMedex, Horsham, PA) twice weekly for an average of 11 treatments to treat scalp LPP in 13 patients. Forty percent of patients had reduced inflammation, and all experienced relief of pruritus. Regrowth was seen in 25% of patients. Tetracyclines can be used with some

success.^{50,212,230} One of the authors (J.S.) uses doxycycline 100 mg twice daily and sometimes combines it with hydroxychloroquine. Complete and sustained remission was reported using rituximab in a young female with juvenile idiopathic arthritis and LPP.²⁵⁶ Low molecular weight heparin has been used with some success in LP, but not specifically in LPP.²⁵⁷⁻²⁶⁸

Frontal fibrosing alopecia

Key points

- Frontal fibrosing alopecia is considered a variant of lichen planopilaris
- Frontal fibrosing alopecia typically occurs on the frontotemporal region of the scalp
- Eyebrow loss is common
- The course of frontal fibrosing alopecia is usually slowly progressive or stable

Considered a variant of LPP,^{1,43} FFA typically occurs on the frontotemporal region of the scalp, but upper periauricular and occipital localization are not uncommon.^{44,45,62} The band of alopecia is often readily distinguishable from the sun-damaged skin of the forehead (Fig 8, A).^{43,45,269} Mild to moderate perifollicular erythema and scaling are visible at the margin of the receded hairline (Fig 8, B and C). Although most common in postmenopausal women, 15% of cases occur in younger women,^{10,29,42,44,62,99,269-272} and FFA may occur in men.^{62,272-275} FFA usually presents in patients who are between 55 and 65 years of age.^{9,10,29,42,44,276} A family history is present in 8% of patients.⁶² Less than 15% of patients will have mucocutaneous LP.^{29,44-46,62,269,270} The loss of the eyebrows is a common and helpful diagnostic feature that affects 50% to 95% of individuals,^{9,10,29,42,43,45,269,271,276,277} and it can either precede or follow the onset of hair loss.^{9,62} The noninflammatory loss of body hairs (primarily of the arms, axillae, pubis, and legs) is relatively



Fig 8. Frontal fibrosing alopecia. **A**, Extensive hairline recession. Frontal fibrosing alopecia is unusual in individuals of African descent. Note the loss of the eyebrows. **B**, Discrete frontal fibrosing alopecia. Note the loss of the eyebrows. **C**, Inflammatory frontal fibrosing alopecia.

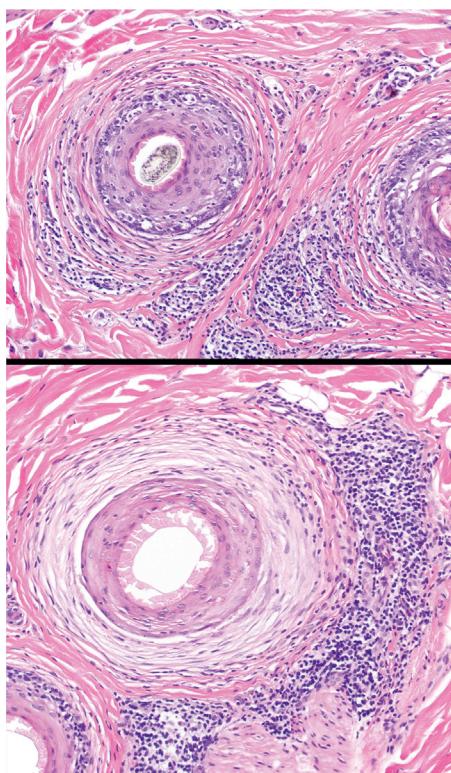


Fig 9. Frontal fibrosing alopecia. Vacuolar interface alteration (top panel) and epithelial/stromal clefting (bottom panel) are characteristic, just as in lichen planopilaris (hematoxylin–eosin stain).

common.^{10,29,42–46,62,270,271,276} This can be difficult to distinguish from physiologic changes occurring after menopause, but biopsy specimens frequently feature the histologic changes of LPP.^{44,45,276} The facial papules sometimes seen in these patients reflect vellus hair involvement.^{62,278} A higher incidence of early menopause and hysterectomy is reported in patients with FFA.^{29,42,62} There are no hormonal laboratory abnormalities.^{42,44,45} FPHL is frequently associated with FFA.^{42,45,62} The differential diagnosis includes alopecia areata, traction alopecia, and FPHL or MPHL.

Little is known about the natural evolution of FFA, but slow progression or spontaneous stabilization is likely.^{9,10,29,42,44,45,62} Eyelash loss, facial papules, and body hair involvement are associated with severe FFA,⁶² while eyebrow loss as the initial presentation may be associated with milder FFA.⁶² In a large series, the majority of women, even with long-standing FFA, had a frontal recession <3 cm, suggesting a spontaneous remission at some point.⁶² Frontal recession can be measured by the distance between the glabella and frontal hairline. The mean glabellar–frontal distance reported in >300 women without hair loss was 5.9 cm.²⁹ In FFA, the distance varies from 6.3 to 12.5 cm, with an average recession of 1.8 to 2.6 cm.^{9,29,45,46} The average rate of frontal hair loss was 0.2 to 2.1 cm per year.^{29,45,62} The distinction between FFA and LPP is primarily clinical, and the histologic findings (Fig 9) are essentially identical.⁴⁴ PDIRS may or may not be present, but often even involved follicles maintain normal inner root sheaths. FFA characteristically spares the interfollicular epidermis.²⁷⁹ Perifollicular inflammation tends to be less intense than in LPP.²⁸⁰

Hormonal replacement therapy is ineffective.⁴⁴ Topical corticosteroids do not appear to be effective, except to reduce pruritus.^{9,44,99,270,281} Topical calcineurin inhibitors may have some efficacy, occasionally permitting regrowth of eyebrows.^{49,98} ITA can allow some regrowth in patients with partial eyebrow hair loss.²⁷⁷ No atrophy was noted in a small series.²⁷⁷ Finasteride and dutasteride are interesting options in postmenopausal women. A few studies have been published using finasteride 2.5 mg for 12 to 18 months, either with or without minoxidil.^{9,10,45,62} Most patients appear to stabilize and sometimes improve (minimal regrowth) with treatment. Photographs and measurement of frontal recession showed an arrest or slowing of progression in a majority of patients^{29,45}; the same is true with dutasteride.^{42,46,49,62} Eyebrow regrowth can be seen. No recurrence was noted in a study with a 6-month

follow-up after discontinuation.⁴⁶ No significant side effects were reported. Dutasteride has a half-life of 5 weeks, and patients can be treated with 0.5 mg weekly.^{42,62} Effective contraception must be used in women of childbearing age. Most patients (50-70%) will have some improvement or stabilize with hydroxychloroquine. Symptoms may be improved while signs of inflammation persist.^{29,42,44,62,229,269} Doxycycline and minocycline can be effective²⁶⁹ and may be considered when the biopsy specimen reveals a sparse infiltrate.^{42,269} Prednisone 25 to 50 mg daily for 1 month appeared to temporarily slow the rapid hair loss in 2 patients, but was of no use in cases with slow progression.⁴⁴ Intramuscular doses of ITA 40 mg every 3 weeks failed to control the disease in 3 patients,⁴⁵ but was beneficial in another case.⁹⁹ Samrao et al²⁶⁹ reported 5 patients treated with mycophenolate mofetil. At 6 months, 1 was a responder, 2 were partial responders, and 2 were nonresponders. Ladizinski et al⁴² reported that 1 of 3 patients stabilized on methotrexate (15-25 mg/wk) after failing to respond to acitretin, azathioprine, interferon-alfa, and pioglitazone.

Graham–Little syndrome

Graham–Little syndrome is an uncommon variant of LPP. It is characterized by LPP on the scalp, nonscarring alopecia of the axillae and pubic areas, and follicular papules on the trunk and extremities.^{2,3} Those features may not be present simultaneously. Women are affected more commonly.²⁸²⁻²⁸⁴ A few reports have been published regarding therapy with topical and intralesional corticosteroids,²⁸⁵ hydroxychloroquine,²⁸² doxycycline,²⁸² cyclosporine,^{285,286} thalidomide,²⁸⁶ and prednisone.^{287,288}

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Primary cicatricial alopecia



Other lymphocytic primary cicatricial alopecias and neutrophilic and mixed primary cicatricial alopecias

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Learning objectives

After completing this learning activity, participants should be able to describe effective strategies for treating each form of scarring alopecias.

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Primary cicatricial alopecias can be frustrating for both patients and physicians. Proper diagnosis guides more successful management of these challenging conditions. Part II will cover the remaining lymphocytic primary cicatricial alopecias, which include pseudopelade of Brocq, central centrifugal cicatricial alopecia, alopecia mucinosa, and keratosis follicularis spinulosa decalvans. It will also discuss the neutrophilic and mixed primary cicatricial alopecias, namely folliculitis decalvans, dissecting cellulitis, folliculitis keloidalis, folliculitis (acne) necrotica, and erosive pustular dermatosis. (J Am Acad Dermatol 2016;75:1101-17.)

Key words: alopecia; cicatricial; fibrosis; follicles; hair; hair loss; lymphocytes; neutrophils; permanent.

PSEUDOPELADE OF BROCQ PATTERN OF CICATRICIAL ALOPECIA

Key points

- **Pseudopelade of Brocq has been described most often in middle-aged white women**
- **Pseudopelade of Brocq is described as a chronic, insidious, slowly evolving condition**
- **Little is known about the management of Pseudopelade of Brocq; the therapeutic**

approach tends to be similar to that of lichen planopilaris

The concept of Pseudopelade of Brocq (PPB) has evolved, and there is no consensus yet as to whether it is a distinct entity¹⁻⁹ or a common final stage of a different primary cicatricial alopecia (PCA).^{8,10-19} In this article, PPB will be discussed because the terminology persists in both the

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Abbreviations used:

AANS:	alopecic and aseptic nodules of the scalp
AM:	alopecia mucinosa
CCCA:	central centrifugal cicatricial alopecia
DC:	dissecting cellulitis
EPD:	erosive pustular dermatosis
FD:	folliculitis decalvans
FK:	folliculitis keloidalis
FM:	follicular mucinosis
FN:	folliculitis necrotica
ITA:	intraleisional triamcinolone acetonide
FKSD:	keratosis follicularis spinulosa decalvans
LPP:	lichen planopilaris
MMF:	mycophenolate mofetil
PCA:	primary cicatricial alopecia
PDIRS:	premature desquamation of the inner root sheath
PDT:	photodynamic therapy
PPB:	pseudopelade of Brocq
TF:	tufted folliculitis

medical literature and clinical practice. However, PPB is probably best considered to be an unusual clinical pattern of cicatricial alopecia, sometimes representing the end-stage of lichen planopilaris (LPP) or other forms of inflammatory alopecia.^{20,21} PPB presents with discrete, smooth, flesh-toned areas of alopecia without follicular hyperkeratosis or inflammation (Fig 1).²⁰ It most commonly affects middle-aged white women (30–50 years of age).^{1,2,6,7,11,18,22,23} It is a chronic, insidious, slowly evolving condition. Plaques may be small, large, scattered, or reticulated, and are usually asymptomatic, but mild pruritus may occur. PPB may affect the beard and eyebrows.^{24–26} The differential diagnosis includes alopecia areata, central centrifugal cicatricial alopecia (CCCA), other burned-out PCAs, syphilis, sarcoidosis, pattern hair loss, and morphea. The histologic features of PPB have nonspecific changes of an end-stage cicatricial alopecia. Follicular scars and loss of sebaceous glands, with variable amounts of residual chronic inflammation, are seen. Little is known about the effective management of PPB. The therapeutic approach tends to be similar to that of LPP. Topical and intralesional corticosteroids and topical tacrolimus 0.1% are used.^{22,23,27–30} Hydroxychloroquine 200 mg twice daily is often used.^{22,23,27,29–33} Response is usually seen within 3 to 6 months; most patients will require 1 to 2 years of treatment.⁸ Oral prednisone 0.5 mg/kg has also been described.^{22,23,27,29–33} Isotretinoin (1 mg/kg/day) and mycophenolate mofetil (MMF; initial dose, 1 g/day) have been reported to have some efficacy.^{22,27,30,31}

CENTRAL CENTRIFUGAL CICATRICIAL ALOPECIA**Key points**

- Central centrifugal cicatricial alopecia is more common in middle-aged women of African ancestry
- Central centrifugal cicatricial alopecia most commonly affects the vertex of the scalp
- Hot comb and relaxers do not appear to be associated with central centrifugal cicatricial alopecia
- Little is known about the management of central centrifugal cicatricial alopecia; the therapeutic approach tends to be similar to that of lichen planopilaris

The concept and terminology of CCCA have evolved. LoPresti et al³⁴ first described the condition as hot comb alopecia. The term follicular degeneration syndrome was subsequently proposed by Sperling and Sau.³⁵ Headington²⁹ suggested “scarring alopecia in African Americans.” Finally, the term CCCA was chosen.^{20,36} It is a descriptive term that includes follicular degeneration syndrome, pseudopelade in African Americans, and central elliptical pseudopelade in whites.²⁰ CCCA is insidious. It predominantly affects middle-aged women of African ancestry,^{23,34,35,37,38} with a prevalence of 3% to 6% in that population.^{39–42} It is uncommon in men^{23,35} and children.⁴³ It most commonly appears on the vertex of the scalp and progresses centrifugally, often symmetrically^{20,23,35,37} (Fig 2). The scalp is soft and pliable.³⁴ Mild perifollicular hyperpigmentation can be seen.³⁵ The affected area gradually blends with the surrounding normal scalp.⁴⁴ Polytrichia^{34,35} and islands of unaffected hair may be present within affected areas.³¹ Tenderness, itching, or burning are usually mild if present.^{35,44–46} A considerable amount of hair is often lost before the alopecia is recognized.³⁵ Although not specific, hair breakage can be an early sign of CCCA.⁴⁷ Its etiology is likely multifactorial. Genetic factors have been suspected,^{40,42,48,49} but this could be caused in part by similar hair care practices within families.⁴² No correlation was found between suspected CCCA and male pattern hair loss in the father.⁴² CCCA is not solely related to the unique shape of black hair because few cases have been described in black men.⁵⁰ Two studies used a questionnaire and standardized photographs⁵¹ to assess CCCA in women of African ancestry (>800 women).^{40,42,51} On a scale of 0 to 5, CCCA was suspected for central hair loss patterns 3 to 5, but was not confirmed histologically. No correlation was found with hot comb usage.^{35,38,40,42,44,52} Relaxers had been used at least once in 90% of women,^{40,42} but



Fig 1. Pseudopelade of Brocq. Small, noninflammatory coalescing plaques.

the great majority of relaxer users do not have CCCA.^{42,46} Although some reports suggested an association of CCCA with relaxers,^{39,43,53} others did not find this association.^{35,38,40,42,44,45,52} There may be a possible association with the long-term use of relaxers.^{39,45,54} The effect of traction hairstyles is unclear.^{38,40,42,45,52} No correlation was found with emollient or styling preparations,⁵² thyroid disease,^{40,42} reaction to hair care products, seborrheic dermatitis, eczema,^{40,42} or hyperandrogenism. Olsen et al⁴² found an association with a history of tinea capitis but not bacterial infection or nonscalp fungal infection.⁴² Conversely, Kyei et al⁴⁰ found an association with a history of bacterial infection but not with scalp or nonscalp fungal infection. The differential diagnosis includes long-standing traction alopecia or trichotillomania, female or male pattern hair loss, alopecia from heat or chemical burn, burnt out discoid lupus erythematosus, LPP, and PPB.^{23,31,34,46}

The earliest histologic finding is premature desquamation of the inner root sheath (PDIRS).^{55,56} This may even be found in normal-appearing scalp skin. PDIRS may not be seen if all abnormal follicles have been destroyed. However, all inflamed follicles have this feature. At the level of the upper isthmus and lower infundibulum, affected follicles show the following (Fig 3): eccentric epithelial atrophy (thinning), with hair shafts in close proximity to the dermis; concentric lamellar fibroplasia of affected follicles; and variably dense lymphocytic perifollicular inflammation.^{19,57-60} Late- and end-stage findings include destruction of the follicular epithelium with retained hair shaft fragments and granulomatous inflammation, replacement of the follicular epithelium by connective tissue, and occasional fusion of infundibula (polytrichia or "tufting"). The histologic differential diagnosis includes early lesions of folliculitis keloidalis (FK).^{61,62} Advanced LPP, like CCCA, can show infundibular inflammation, superficial perifollicular fibrosis, and destruction leading to free hair shafts within the

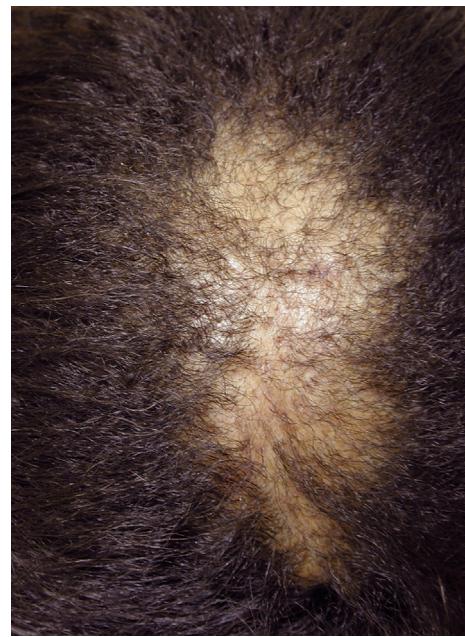


Fig 2. Central, centrifugal cicatricial alopecia. Symmetrical alopecia centered on the crown/vertex of the scalp.

dermis. Vacuolar interface dermatitis, if still present, is evidence of LPP; LPP does not show PDIRS in noninflamed follicles.⁶³ PDIRS may be found as a nonspecific feature in heavily inflamed follicles in any disease state, so it must be interpreted in the context of other clinical and histologic findings.⁶⁴

The literature is scant regarding the management of CCCA, and treatments are empiric. Despite lack of evidence of efficacy, minimal hair grooming is recommended.^{23,49,52} Shampooing at least once a week is recommended to reduce symptoms and treat seborrheic dermatitis.^{49,65} Topical steroids and intralesional triamcinolone acetonide (ITA) are often first-line therapy.^{23,37,44,46,52,65} Lower concentrations reduce the risk of hypopigmentation in dark-skinned patients.⁴⁶ Topical or systemic antibiotics—mostly doxycycline—are suggested,^{23,37,44,46,66} and they are continued until improvement is seen (2-6 months), then the dose is reduced and eventually discontinued when the condition has been quiescent for a full year.⁴⁴ Minocycline is less commonly used due to the risk of severe hypersensitivity reaction.⁶⁷⁻⁷⁰ Hydroxychloroquine,⁴⁹ MMF, and cyclosporine have also been reported.⁴⁹ Short courses of oral corticosteroids can be used in cases of active inflammation.⁴⁶ The absence of inflammation on scalp biopsy specimens should be confirmed before hair transplantation is considered.⁶⁵ Even though the risk of keloid is low⁶⁵ and curly black hair usually offers better coverage than the hair of white patients,⁶⁵ graft survival and regrowth is low.^{37,71} A test graft session is recommended before proceeding.⁶⁵

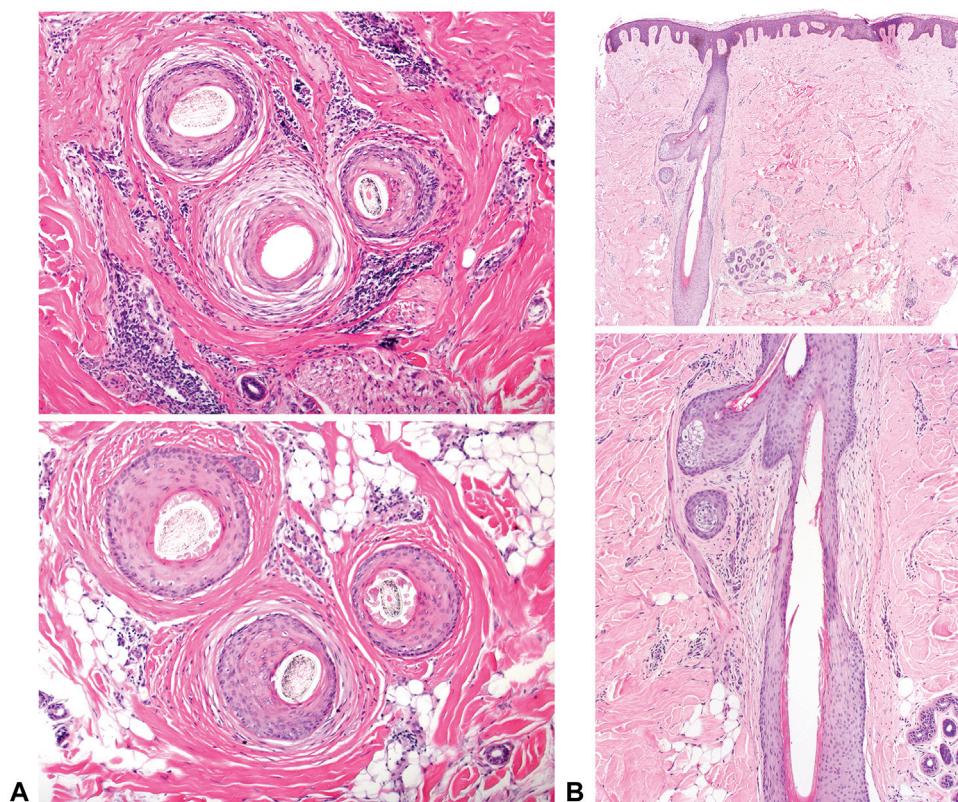


Fig 3. Central, centrifugal cicatricial alopecia. Horizontal (**A**) and vertical (**B**) sections showing premature desquamation of the inner root sheath, eccentric epithelial atrophy, concentric lamellar fibroplasia, and chronic perifollicular inflammation. (Hematoxylin–eosin stain.)

ALOPECIA MUCINOSA/FOLLICULAR MUCINOSIS

Key points

- Alopecia mucinosa is rare
- Long-term follow-up and obtaining multiple biopsy specimens over time are advised
- There is no specific treatment

The terms follicular mucinosis (FM) and alopecia mucinosa (AM) are often used interchangeably in the literature. FM is the accumulation of mucin within the hair follicle. It is nonspecific and is seen in numerous conditions.^{72,73} AM is alopecia associated with FM.⁷⁴ AM is usually noncicatricial and reversible. Cicatricial AM is exceedingly rare.²³ There is no specific treatment. Some cases resolve spontaneously within months to years.^{73,75} Treatments proposed have variable success rates and are mostly anecdotal.^{23,31,74,76-89} AM may be associated with mycosis fungoides (MF) or Sézary syndrome (SS), especially in elderly patients.^{75,90-101} The onset of malignancy can precede, coincide, or follow the alopecia.⁹⁷ Long-term follow-up is advised, and obtaining multiple biopsy specimens over time may be necessary to establish a diagnosis.^{73,90}

KERATOSIS FOLLICULARIS SPINULOSA DECALVANS

Key points

- Keratosis follicularis spinulosa decalvans is often not recognized
- Keratosis follicularis spinulosa decalvans is a rare genetic form of scarring alopecia
- Keratosis follicularis spinulosa decalvans usually begins in early childhood with keratosis pilaris
- Ophthalmologic examination is recommended

Keratosis follicularis spinulosa decalvans (KFSD) is a rare genetic form of scarring alopecia. The diagnosis is often delayed because it is not recognized.¹⁰² It falls within the broader spectrum of keratosis pilaris atrophicans along with atrophoderma vermiculatum and keratosis pilaris atrophicans faciei. It was originally described as X-linked, but autosomal dominant and sporadic cases have been reported.¹⁰³⁻¹¹⁰ KFSD usually begins in early childhood with keratosis pilaris on the face, progressing to the trunk and extremities. Cicatricial alopecia of the scalp and eyebrows/eyelashes eventually develops. Other common features include hyperkeratosis of the palms and



Fig 4. Folliculitis decalvans. **A**, Tufted hairs. **B**, Pronounced inflammation and hyperkeratosis.

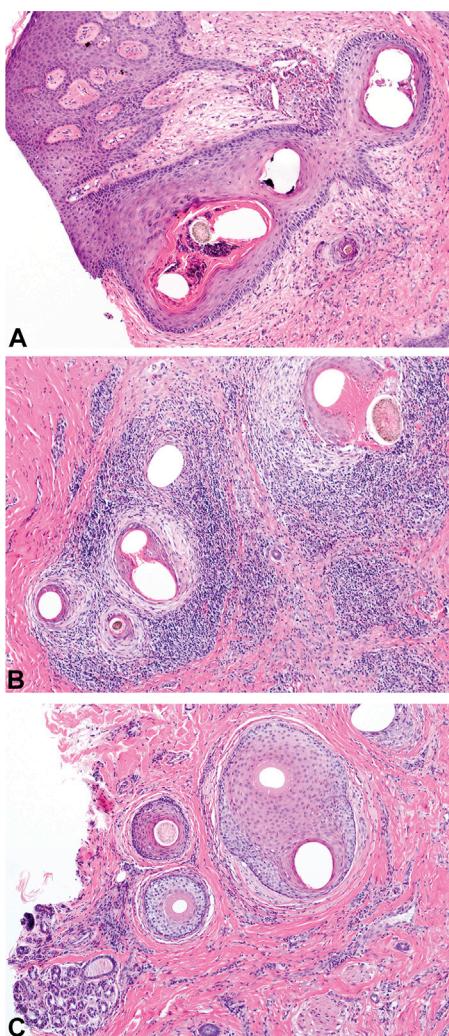


Fig 5. Folliculitis decalvans. Polytrichia is evident (**A**) and inflammation is most intense at the level of the upper isthmus and infundibulum (**B**). The lower portions of the follicles (**C**) are relatively spared, in contrast to dissecting cellulitis. (Hematoxylin–eosin stain.)



Fig 6. Dissecting cellulitis presents with a few to many nodules.

soles, photophobia, and corneal abnormalities. Ophthalmologic examination is recommended. Both exacerbation and improvement have been reported at puberty. The clinical presentation in girls is usually milder in X-linked cases.^{102,104,105,111-113} Other clinical differences have been noted between X-linked and sporadic autosomal dominant cases (eg, age of onset and symptom severity), and the term folliculitis spinulosa decalvans has been proposed for autosomal dominant forms of KFSD.¹¹⁴ but the small number of published cases do not allow for clear phenotypic differentiation.¹⁰⁴ The differential diagnosis includes atrichia with papular lesions, atrophoderma vermiculata, keratosis pilaris rubra atrophicans faciei (ulerythema ophryogenes), ichthyosis follicularis-alopecia-photophobia syndrome, and keratitis ichthyosis and deafness syndrome. Most of these conditions are usually not associated with scarring alopecia of the scalp. In adults, Graham–Little syndrome, LPP, and folliculitis decalvans (FD) may be considered.^{102,115} Early management is important,

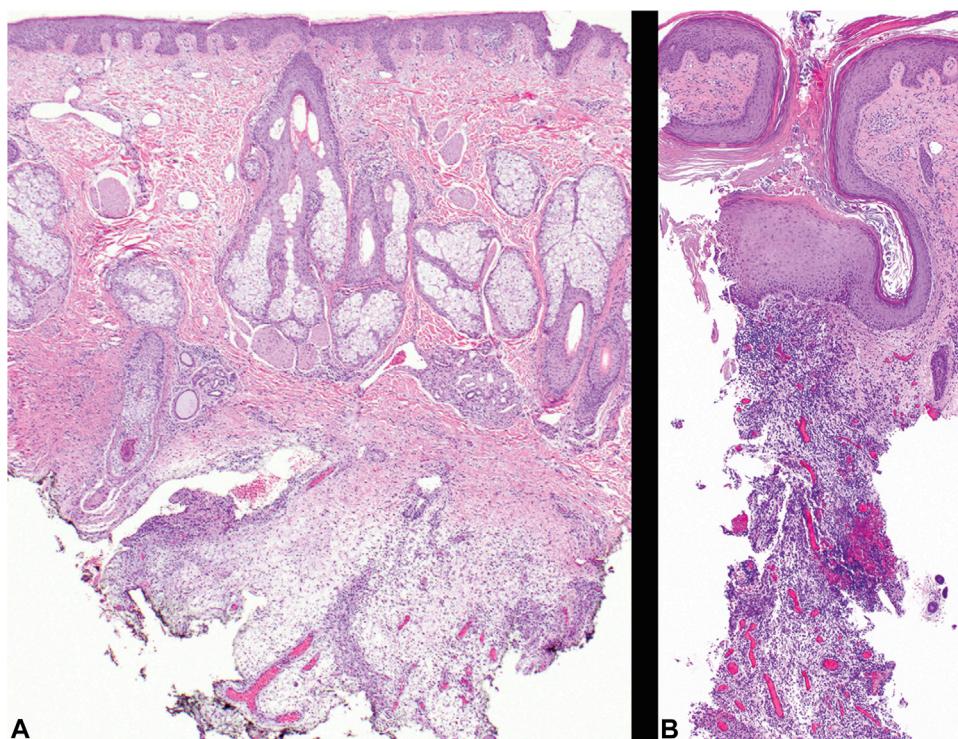


Fig 7. Dissecting cellulitis of the scalp. Vertical sections show deep-seated intense inflammation. In early disease, sebaceous glands are still preserved (**A**), but eventually they are destroyed and sinus-tract formation occurs (**B**). (Hematoxylin–eosin stain.)

although not many patients will improve.¹¹⁶ Keratolytics, such as salicylic acid or urea, may improve the appearance of the skin.¹¹³ Topical and intralesional corticosteroids may reduce inflammation.^{102,113,117} Both isotretinoin and etretinate have been reported to be successful when the condition is inflamed.^{102,113,117,118} Oral antibiotics,¹¹³ dapsona,¹⁰⁹ and laser hair removal¹¹⁹ have reportedly been useful.

FOLLICULITIS DECALVANS

Key points

- **Folliculitis decalvans commonly affects middle-aged men**
- **Folliculitis decalvans usually presents on the vertex and occiput of the scalp**
- **Folliculitis decalvans usually presents with an indurated scalp, tufted hair, and crusts**
- **Systemic antibiotics are commonly used**

FD most commonly affects middle aged men.^{22,23,120-124} It usually presents on the vertex and occiput of the scalp, but it has been noted in other locations, including the face and neck. Multifocal lesions have been described.^{22,120,123,125,126} Follicular papules and pustules characterize FD, but they are not always present on examination. The lesions may be painful or pruritic, and affected areas of the scalp are inflamed and feel thickened and indurated. Tufted

hair and crusting are frequently seen (Fig 4). Tufted hair is the emergence of several hair shafts through a single follicular orifice and has the appearance of doll's hair. There is controversy regarding whether tufted folliculitis (TF) is a manifestation of different cicatricial alopecias or a distinct clinical entity.^{15,127-133} No difference in presentation, clinical course, causative organisms, histology, lymphocytes involved, or response to treatment were found by Powell et al,¹²⁸ which suggest that they are part of a similar process rather than 2 different conditions. The authors do not believe TF is a distinct entity, because it has been reported in folliculitis keloidalis (FK), dissecting cellulitis (DC), tinea capitis, pemphigus of the scalp, discoid lupus erythematosus, CCCA, and LPP.^{15,23,129-131,133-135} The differential diagnosis of FD includes bacterial folliculitis, tinea capitis, deep fungal infections, DC, FK, erosive pustular dermatosis (EPD), LPP, and CCCA. Bacterial/fungal cultures should be performed and a biopsy specimen of the scalp should be obtained if needed to rule out other conditions, especially tinea capitis. It has been suggested by some authors that FD represents a pattern of inflammation that can be seen in several forms of cicatricial alopecia, especially CCCA.⁵⁷ This concept is controversial and has yet to be resolved.¹³⁴ The exact role of *Staphylococcus aureus* when present in the pathogenesis of FD is unclear. The persistence of

S aureus after good clinical response to topical tacrolimus suggests an abnormal inflammatory response to *S aureus*.¹³⁶

Histologically, polytrichia (fused infundibula) and peri- and intrafollicular neutrophils are commonly seen (Fig 5, top panel); mixed acute and chronic inflammation with follicular damage is most intense in the upper half of the dermis (middle panel) with relative sparing of the deeper dermis (bottom panel).

Topical antibiotics (eg, mupirocin, fusidic acid, erythromycin, or clindamycin) may be used alone or in combination with topical or intralesional corticosteroids for milder cases or as maintenance therapy.^{120,137} Topical triclosan is generally considered safe,¹³⁸⁻¹⁴² but there are concerns regarding its safety in humans.¹⁴³⁻¹⁴⁶ Oral antibiotics are probably used most frequently, and the duration of treatment varies from a few weeks to 1 year.^{120,123,147-149} The classic combination of rifampicin 300 mg twice daily with clindamycin 300 mg twice daily for 10 weeks can be effective.^{128,135,150} Alternatives to clindamycin include ciprofloxacin, clarithromycin, tetracyclines, and topical mupirocin.^{123,128,135,137,150} Rifampicin is rarely used alone because of the rapid emergence of resistance.¹⁵¹ Little is known about the effect of these combinations, and the data come primarily from in vitro studies.¹⁵¹⁻¹⁵³ Rifampicin is a potent inducer of the cytochrome P450 (CYP3A4) enzymes, while clindamycin inhibits the same cytochrome.^{151,154} Tetracyclines are used for the treatment of FD, and mild cases tend to have better responses.^{120,123,147,148} Adjuvant treatment with either zinc gluconate or oral glycyrrhizin have been reported to help.^{120,155} Isotretinoin can be used to treat FD in dosages from 0.5 to 1 mg per kg per day, sometimes combined with systemic corticosteroids or antibiotics.^{121,148,150,156} Isotretinoin is not effective in our experience. Dapsone (75-100 mg/day) can be effective, but maintenance treatment using 25 mg daily may be necessary to avoid relapse.^{122,123} Good response with long-term remission was seen with the use of both zinc sulfate and oral fusidic acid.^{123,149,150,157} Acitretin,¹²⁰ oral L-tyrosine,¹²⁴ laser hair removal,^{119,158,159} photodynamic therapy (PDT),¹⁶⁰ and a low dosage of 440-cGy x-rays¹⁶¹ have been used with some success.

DISSECTING CELLULITIS

Key points

- Dissecting cellulitis affects predominantly young men of African descent
- Most patients respond well to isotretinoin or antibiotics
- Alopecic and aseptic nodules of the scalp should be kept in mind as a differential diagnosis

DC is uncommon and affects predominantly young men (15-40 years of age) of African descent.^{119,162-187} DC presents with few to multiple firm or fluctuant nodules, sometimes forming abscesses and sinus tracts.^{162,164,165,171,173-176,178} Either pus or serous liquid may be present with spontaneous or elicited drainage.^{164,173-176} Pustules and crusting can be seen. Lesions may have a cerebriform configuration. It most commonly affects the vertex or back of the scalp,^{119,162,165,171-174,177,179,182} but may affect other areas^{164,165,171,172,175,178} (Fig 6). Lesions can be painful, sometimes requiring analgesics.¹⁶⁴ Cervical lymphadenopathy, if present, usually resolves when the condition is controlled.^{164,174} Bacteriologic and mycologic cultures are almost always negative.^{165,167,168,171,173-176,178,179,182,188} The classic follicular occlusion triad is rarely seen,^{164,166,178,189} and most reports are unassociated with acne conglobata or hidradenitis suppurativa. The association with seronegative arthritis is well established but uncommon, and African Americans are predominantly affected. Skin manifestations usually precede the arthritis, and there is often a temporal relationship between flares in joint and skin diseases. Rheumatoid factor and HLA-B27 are usually negative.¹⁸⁹ Anecdotal reports of association with keratitis ichthyosis and deafness syndrome, musculoskeletal disorders, and pyoderma vegetans have been published.^{163,172,190-193}

The differential diagnosis includes FD, FK, tinea capitis/kerion, and cutis verticis gyrate.^{23,194} DC is frequently misdiagnosed as cysts. A new entity, alopecic and aseptic nodules of the scalp (AANS), has been proposed by Abdennader et al¹⁶² following reports of pseudocysts of the scalp.¹⁹⁵⁻¹⁹⁷ AANS is uncommon, and in contrast to DC it affects predominantly young (19-35 years of age) white or Asian males. Most patients with AANS have 1 or 2 firm, dome-shaped nodules on the occiput or vertex of the scalp. The alopecia is nonscarring and the surrounding scalp is normal. Puncture of the nodule yields hemorrhagic, yellowish, or purulent aseptic material. The majority of patients respond to doxycycline 100 mg daily for 3 months. Puncture or obtaining a biopsy specimen sometimes leads to resolution of a nodule. Biopsy specimens obtained from early lesions of DC (Fig 7) feature a deep peribulbar and subfollicular lymphocytic infiltrate.¹⁹⁸ Well-developed lesions (usually fluctuant nodules) feature deep perifollicular and lower dermal abscesses composed of lymphocytes, neutrophils, and plasma cells.⁵⁹ Catagen/telogen hairs are increased in number. Although sebaceous glands remain intact early in the course of the disease, eventually they are destroyed. In late-stage lesions, granulation tissue

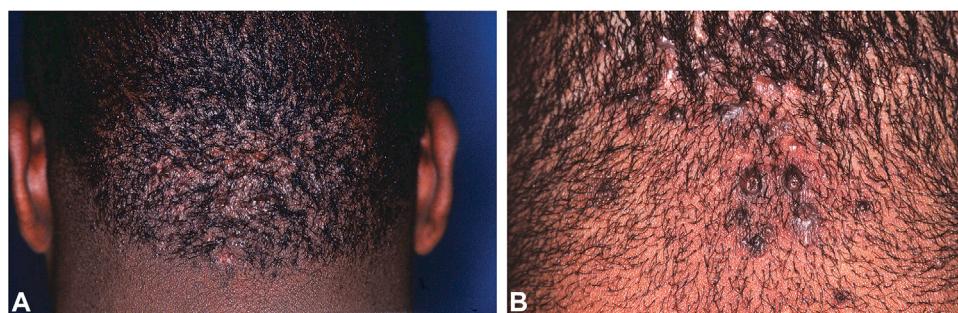


Fig 8. Folliculitis keloidalis. **A**, Early involvement. **B**, Close view of fibrotic papules.

and epithelial-lined, true sinus tracts dominate the picture. The histologic findings are fairly characteristic, but tinea capitis can occasionally mimic DC both clinically and histologically.^{194,199,200} Special stains for fungal organisms (eg, Grocott methenamine silver or periodic acid-Schiff) combined with cultures will help rule in or rule out tinea. FD is characterized by superficial inflammation (upper half of follicles)^{60,201}; DC is a much deeper process (ie, the lower half of follicles and superficial fat).

Treatments for DC include topical isotretinoin 0.05% and clindamycin 1%.¹⁷⁹ The use of various systemic antibiotics, including tetracyclines, is usually ineffective.^{22,119,166,168,170,172,173,182} Most patients respond well to isotretinoin (0.5-1 mg/kg/day) with sustained remission and regrowth for months to years after discontinuation.^{22,30,165,168,173,175,177} A starting dose of 1 mg per kg per day is suggested, and treatment should be continued for ≥ 4 months after the disease is in remission to reduce the risk of recurrence.^{173,174,177,202,203} Higher doses and a longer period of time seem necessary to treat DC compared to acne.¹⁸⁸ Isotretinoin is resumed in cases of relapse. A good response was seen with oral prednisolone,^{119,182} and adalimumab^{171,204} and infliximab^{164,205} were reported to be effective in unresponsive cases of DC with regrowth and prolonged remission. Response is seen within 2 months, but treatment needs to be continued. Etanercept was ineffective.¹⁶⁶ Laser depilation appears effective, with prolonged remission in recalcitrant cases.^{119,167,172,204} Local anesthesia may be necessary, and persistent hypopigmentation may occur.^{119,167} External beam radiation therapy was effective in unresponsive cases with complete and sustained remission and good cosmetic outcome. Acute cutaneous side effects were mild, and no long-term sequelae have been observed. The benefits may outweigh the risks associated with radiation therapy in some cases.¹⁶⁹ Surgery with complete scalp excision to the galea followed by split-thickness skin grafting was effective in severe, nonresponsive cases.^{166,178,183} A good response was reported in 1 patient using alitretinoin up to 20 mg daily.²⁰⁶ Acitretin

20 mg failed in 1 patient, and a higher dose was not tolerated.²⁰⁶ Zinc was reported to be both effective¹⁷⁰ and ineffective.^{173,182} Dapsone,^{119,172,182} colchicine,¹⁷² azathioprine,¹⁷² methotrexate,¹⁷² and PDT²⁰⁶ were ineffective.

FOLLICULITIS KEOIDALIS

Key points

- **Folliculitis keloidalis usually affects young men of African descent**
- **Folliculitis keloidalis presents almost exclusively on the occiput of the scalp**
- **Association with localized trauma or friction has not been proven**

FK presents with papulopustules and fibrotic papules/nodules almost exclusively on the nape of the neck and the occiput of the scalp^{66,207-210} (Fig 8). Involvement of the vertex and parietal scalp is uncommon.^{66,209,211} Lesions may coalesce into horizontal keloid-like plaques and, rarely, chronic abscesses.^{66,207-210} Comedones are not found.²¹⁰ Tufted hair can be seen.²¹⁰ Pruritus, burning, or pain may be present.^{66,210} FK usually affects young men of African descent.^{43,66,209,210} It is uncommon in women, children, and other races.^{39,43,66,207,210,212-215} The etiology of FK remains unclear. In a retrospective study, Khumalo et al²¹⁶ concluded with the need to clarify the extent to which mechanical haircut-associated injuries cause FK. Other studies found no association with the use of clippers or blades, and there usually is no family history of FK or personal history of keloid formation.^{39,66,209,213} The association with localized trauma or chronic irritation is mostly circumstantial and has not been proven.⁶⁶ The exact role of seborrhea and increased serum testosterone is unknown, as well as the significance of more numerous dilated blood vessels and mast cell populations that were found in the occipital scalp compared to the frontal scalp.^{66,209} Contrary to pseudofolliculitis barbae, ingrown hairs do not play a role in the etiology of FK.⁶⁶ Acneiform eruptions (50%) and

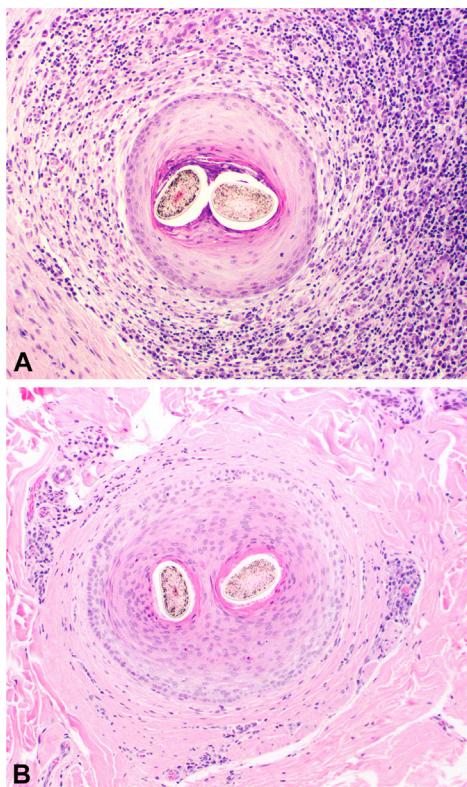


Fig 9. Folliculitis keloidalis. Early lesions (inflamed papules) show a chronic perifolliculitis (without vacuolar interface change) of the upper isthmus and infundibulum (**A**). Premature desquamation of the inner root sheath may be present (**B**). (Hematoxylin–eosin stain.)

pseudofolliculitis barbae (33%) are common.^{209,211} No difference in *Propionibacterium acnes* population has been found.²⁰⁹ A few cases have been reported with acanthosis nigricans, but were not associated with metabolic syndrome.²¹⁷ The differential diagnosis include folliculitis, tinea capitis, keloids, acne mechanica, FD, molluscum contagiosum, sarcoidosis, and DC.^{210,218}

Histologically, one typically finds perifollicular lymphocytic and plasmacytic inflammation (ie, periinfundibular and periisthmic) in combination with perifollicular lamellar fibroplasia (particularly periisthmic) in early lesions of FK (Fig 9). Other common findings are: disappearance of sebaceous glands in involved follicles; thinning of the follicular epithelium; PDIRS; follicular destruction with resulting “naked” hair shafts in the dermis; and follicular scarring. These naked hair shafts lead to the hypertrophic scarring found in keloidal stages of the disease. Vacuolar interface alteration of the follicular epithelium is not found. Biopsy specimens obtained from clinically noninvolved areas may feature follicular inflammation or scarring. None or few organisms are identified using special

stains, indicating that bacterial overgrowth is not important in the pathogenesis. FK, CCCA, and FD can show essentially identical histologic findings, which suggests a relationship between these diseases. The distinction between them primarily depends on clinical correlation.⁶⁶

Management includes avoiding friction (eg, hats, helmets, and collared shirts), although its significance is unknown.^{207,209,219} Daily use of antibacterial or keratolytic shampoo may be useful, as are topical antibiotics.^{23,66,207,220,221} When used, ITA injections (3–40 mg/cm²)^{66,211,213,214,221} should be made directly into raised papules.²⁰⁷ Transitory hypopigmentation may occur after injections.²¹⁰ Cryotherapy can be used to reduce fibrotic papules or to facilitate intralesional injections, but hypopigmentation is a risk, and a freeze/thaw time of <25 seconds should be used.^{207,210} Topical retinoids may help flatten existing lesions.^{207,210} Imiquimod for 5 to 7 days for 8 weeks has been successful in some patients.²¹⁰ Topical and systemic antibiotics—primarily tetracyclines and erythromycin—can be helpful.^{66,207,210} A higher dose is used initially, followed by a lower maintenance dose in accordance with clinical response and relapse rates (eg, doxycycline 100 mg twice daily followed with 50 mg daily).²⁰⁷ Isotretinoin has been useful in some cases, but not all.^{207,222–224} Deep excision (up to subcutaneous or muscle fascia) in ≥1 multiple stages with primary closure offers good to excellent cosmetic results in the majority of patients.^{22,225} Tissue expansion can be useful.²²⁶ No complete recurrence has been reported, but many patients eventually develop new lesions. Hypertrophic scars may occur in a minority and can be treated with high-potency or intralesional steroids immediately after complete healing.^{210,225} Excision with secondary healing is also an option.²²⁷ Healing time varies from 6 to 10 weeks, and the cosmetic results are fair to good.²²⁷ Better results with faster healing and better tissue contraction may be achieved with a horizontal ellipse that includes the posterior hairline.²²⁸ Skin grafting for closure offers no cosmetic benefits in most cases.^{229–231} Removing individual papules with a punch extending deep into the subcutaneous tissue with primary or secondary healing has also been described.²¹⁰ Recurrence is high with shaving or superficial excision.²¹⁰ Long-pulsed neodymium-doped yttrium aluminium garnet lasers can significantly improve both clinical and histopathologic features of FK in most patients and can stop the disease process if followed by maintenance sessions. Early cases respond better.²³² Diode laser is also effective.^{229,233} Electrodessication and abrasion with CO₂ lasers are ineffective.^{229,234} Radiation therapy is not recommended.²³⁴



Fig 10. Erosive pustular dermatosis. **A** and **B**, Note the beefy red inflammation. **C**, Posttreatment.

FOLLICULITIS NECROTICA

Key points

- Folliculitis necrotica is rare
- Folliculitis necrotica usually affects adults
- Folliculitis necrotica is a chronic, relapsing condition involving the anterior hairline and seborrheic areas

Folliculitis necrotica (FN) is rare. Two forms are described: FN varioliformis and FN miliaris. Only FN varioliformis results in cicatricial alopecia. FN usually affects adults and is a chronic, relapsing condition involving the anterior hairline and seborrheic areas of the face and trunk.^{23,235-237} Episodes of reddish-brown papulopustules appear, undergo central necrosis, and eventually leave depressed, punched-out scars.^{23,235-237} Exacerbation in the summer months has been reported.²³⁶ The differential diagnosis includes folliculitis, molluscum contagiosum, herpes zoster, eczema herpeticum, neurotic excoriations, and acne necrotica miliaris. A positive culture may influence therapy.²³⁸ Topical and intralesional corticosteroids may help.^{23,236} Various systemic antistaphylococcal antibiotics, including tetracycline, can be effective.^{23,235,236,238,239} Isotretinoin has also been reported to be a successful treatment.^{236,238}

EROSIVE PUSTULAR DERMATOSIS

Key points

- Erosive pustular dermatosis is rare
- Erosive pustular dermatosis usually affects elderly patients

- A beefy red coloration is characteristic
- Oral prednisone is often effective
- Long-term remission can be expected

EPD is a rare form of PCA characterized by erosion, crusting, and pustular lesions on the scalp. A beefy red coloration is characteristic (Fig 10). It generally occurs in elderly patients,²⁴⁰⁻²⁵¹ but it may affect younger patients^{244,249,252-255} and, rarely, children.²⁵⁶⁻²⁵⁸ White patients and women are affected most commonly.^{244,245,247-250} The etiology is unclear, but it has been reported after local trauma, such as surgical procedures, exposure to ultraviolet light, sunburn, radiotherapy, herpes zoster, and after the treatment of AK with fluorouracil, imiquimod, cryotherapy, and PDT. The lag period between trauma and appearance of EPD varies greatly, from weeks to years.^{240-243,248,251,253} Autoimmune conditions have been reported in association with EPD (eg, rheumatoid arthritis, autoimmune hepatitis, Hashimoto thyroiditis, and Takayasu arteritis), but their significance is unknown.^{248,259} The differential diagnosis is broad, as would be expected for an erosive skin condition.^{244,252,253}

The histologic findings in EPD (Fig 11) are suggestive but not specific, and therefore good clinical correlation is required to establish the diagnosis. Typically, one sees marked epidermal atrophy with focal erosions. There is an upper dermal mixed inflammatory infiltrate consisting predominantly of neutrophils, lymphocytes, and especially plasma cells. Intraepidermal accumulations of neutrophils are often present. The diagnosis

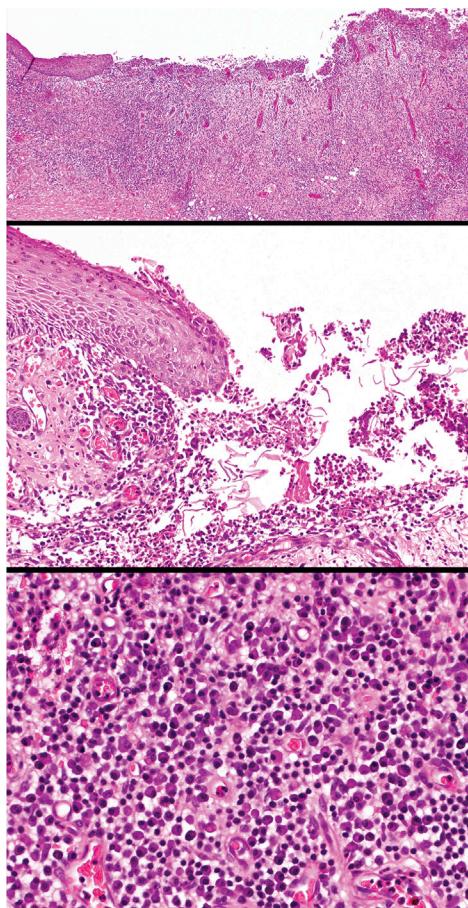


Fig 11. Erosive pustular dermatosis. Epidermal atrophy and an intense, mixed inflammatory infiltrate are present. Slide courtesy of Dr Almut Böer-Auer. (Hematoxylin–eosin stain.)

of EPD is usually made by excluding other conditions.

Most reported cases respond well to therapy, with a generally sustained remission. The improvement is often rapid (within 3–7 days) and EPD resolves within 2 weeks to 4 months of treatment.^{240–244,246,250,252–254} Maintenance therapy with topical tacrolimus can be effective in cases of relapse.²⁴³ Topical and oral antibiotics and anti-fungals are usually ineffective, unless there is a secondary infection.^{243–245,250,252,254,255} Topical treatment with potent topical corticosteroids twice daily^{243,245,249,260} and topical tacrolimus 0.1% either 1 or 2 times daily are often effective,^{240,243,246,247,261,262} but not always.^{250,252,254,255} Tacrolimus may be difficult to tolerate for some patients.²⁵⁰ Topical calcipotriol was effective in a case report.²⁶³ Topical dapsone was effective in 4 patients, most of whom had failed previous topical and systemic therapy.²⁵⁴ Oral prednisone (15–40 mg/day) for ≤4 weeks that is then tapered is often

effective.^{242,244,246,254,264} Most cases reported to have failed prednisone used a lower dosage or a shorter duration of treatment.^{252,254} Other options include doxycycline (200 mg/day),²⁵³ oral isotretinoin (0.75 mg/kg/day),²⁵² oral acitretin (50 mg/day),²⁵⁰ oral dapsone (\leq 100 mg/day),^{245,254} and oral zinc (180–600 mg).^{255,265} Treatment is maintained until remission is achieved and then slowly tapered and discontinued. Oral nimesulide may help reduce the pain but does not generally improve the condition.^{249,252} PDT^{241,251,264,266} and surgery²⁴⁸ have been reported to both trigger and treat EPD, and should therefore be used with caution and only as a last resort.

In conclusion, PCAs are composed of different entities, each with its own characteristics. It is essential to recognize PCAs early so that the best possible treatment plan can be implemented. PCAs can be frustrating for both patients and clinicians. The information contained in this continuing medical education article should enable clinicians to better comprehend PCAs and offer adequate information, treatment, and support to patients with PCAs.

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Answers to CME examination

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