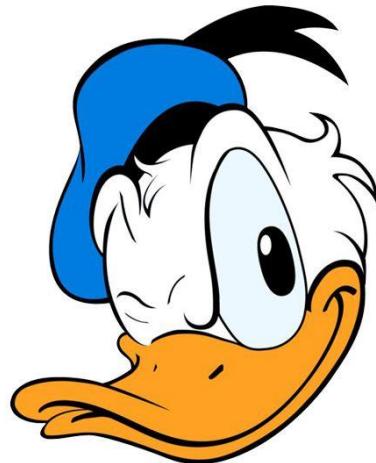


DERMATOLOGY

CME

2014





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Diabetic foot ulcers

Part I. Pathophysiology and prevention

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Learning Objectives

After completing this learning activity, participants should be able to assess the epidemiology of diabetes mellitus and its complications; identify the high risk diabetic foot; delineate diabetic foot ulcer (DFU) prevention strategies; outline the pathophysiology of a DFU; review factors associated with delayed DFU healing (suboptimal diabetes control with elevated HbA1c levels, vascular compromise, increased bacterial burden or deep and surrounding infection, increased plantar pressure due to neuropathy and foot deformities.); and describe clinical characteristics and stage of DFUs based on depth and causative factors.

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Diabetes mellitus is a serious, life-long condition that is the sixth leading cause of death in North America. Dermatologists frequently encounter patients with diabetes mellitus. Up to 25% of patients with diabetes mellitus will develop diabetic foot ulcers. Foot ulcer patients have an increased risk of amputation and increased mortality rate. The high-risk diabetic foot can be identified with a simplified screening, and subsequent foot ulcers can be prevented. Early recognition of the high-risk foot and timely treatment will save legs and improve patients' quality of life. Peripheral arterial disease, neuropathy, deformity, previous amputation, and infection are the main factors contributing to the development of diabetic foot ulcers. Early recognition of the high-risk foot is imperative to decrease the rates of mortality and morbidity. An interprofessional approach (ie, physicians, nurses, and foot care specialists) is often needed to support patients' needs. (J Am Acad Dermatol 2014;70:1.e1-18.)

Key words: diabetes; diabetic foot ulcer; neuropathy; wounds.

The number of people with diabetes mellitus (DM) has increased dramatically. DM is a serious, lifelong condition that is the seventh leading cause of death in North America.¹ Persons with DM have a 15% to 25% chance of developing a diabetic foot ulcer (DFU) during their lifetime, and a 50% to 70% recurrence rate over the ensuing 5 years.²⁻⁴ Early detection and effective management can reduce the severity of complications, including preventable amputations. Dermatologists assessing and treating patients with DM and DFUs can benefit from an interprofessional team to optimize patient management and outcomes.

THE BURDEN OF DIABETES MELLITUS AND COMMON DIABETIC COMPLICATIONS

Key points

- More than half of persons with diabetes mellitus are unaware of their disease
- 2.5% to 15% of annual global health care budgets are spent on diabetes mellitus
- Diabetes mellitus is the seventh leading cause of death in the United States
- Diabetes mellitus is the leading cause of kidney failure, nontraumatic lower extremity amputations, and new cases of blindness in adult Americans
- Diabetic foot ulcers are often preventable, and treatment is frequently suboptimal

DM is an increasing problem in both developed and developing nations. The majority of persons with DM have type 2 DM, with only 5% to 10% of patients diagnosed with type 1 DM.^{5,6} Several studies

have concluded that >50% of people with DM (according to World Health Organization criteria) are unaware of their disease.^{7,8} Early DM detection and treatment can improve overall quality of life (QOL) and increase the life expectancy of persons with DM. The prevalence of DM is also increasing. For example, in North America, DM affects up to 20% to 25% of the elderly population over 65 years of age.^{1,9} Worldwide estimates have calculated that 2.5% to 15% of global annual health care budgets are spent on DM, and the annual direct medical cost worldwide is as high as \$241 billion.⁷

In their 2009 report, the Canadian Diabetes Association labeled the increased prevalence of DM an "economical tsunami," with a doubling of the number of people diagnosed in the past decade.¹⁰ In 2010, 26.9% of US residents above 65 years of age (10.9 million) had DM.¹ DM is the leading American cause of kidney failure, non-traumatic lower extremity amputations, and new cases of adult blindness.¹

DM is a serious, lifelong metabolic condition that is the seventh leading cause of death in North America.¹ By 2025, it is predicted that ≥333 million people will develop DM worldwide; this increase creates growing health and economic issue.¹¹⁻¹³ In the developing world, the rise in the number of persons with DM will have a devastating negative impact on health care systems and individual health.¹ Every year, 1 million people worldwide lose their lives to DM-associated complications, with most of these deaths being preventable.⁷

Chronic wounds, including DFUs, are a common yet challenging problem. These ulcers often display

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suboptimal healing particularly when the underlying disease and cause have not been treated and the patient has not received holistic interprofessional care.

The importance of routine foot examination in persons with DM and the identification of the high-risk foot are underestimated in both inpatient and outpatient settings because of the asymptomatic nature of the disease. There is often a reluctance to conduct foot screening for patients with DM because of a perceived lack of time in busy practices.¹⁴ The early recognition of the high-risk foot and timely treatment may prevent foot ulcers, save limbs, potentially save lives, and improve patient QOL. These individuals often have a history of previous foot ulcer or lower limb minor or major amputation.

Once a foot ulcer develops, optimal care for persons with DFU includes the assessment of adequate arterial blood supply to heal, the assessment of neuropathy, and the diagnosis and treatment of infection.

Many of the requirements for holistic DFU care are beyond the expertise of the practicing dermatologist. There is also often an overall lack of interprofessional networking required for optimal management.¹⁵ This gap is related to a lack of knowledge, routine practice procedures, and health care organizational barriers.

RISK OF DIABETIC FOOT ULCERS AND LOWER LIMB AMPUTATIONS

Key points

- Diabetic foot ulcers precede 85% of lower limb amputations
- Diabetic foot ulcers are the most costly and preventable complication of diabetes mellitus
- The average lower limb amputation and rehabilitation costs \$44,790

DM has a vast range of short- and long-term complications, and up to 85% of nontraumatic lower extremity amputations are attributed to DM.¹⁶⁻¹⁸ A foot ulcer diminishes QOL. Persons suffering from a nonhealing DFU have approximately 10% to 40% lower QOL scores than the general population. For example, the DFU impact on QOL is equivalent to chronic lung disease, myocardial infarction, and breast cancer.¹⁹⁻²¹

The development of DFU and the subsequent, often preventable nontraumatic lower extremity amputations are among the most costly complications of DM. A Canadian study on the cost of complications of DM found that major events,

including lower limb amputations, generate a greater financial burden than DFU treatment alone.²² The rate of foot ulcer development in persons with diabetic neuropathy is increased, and peripheral neuropathy is the most significant risk factor for DFU.²³⁻²⁵ Once an ulcer develops, healing is often slow, with the average estimate being >2 months for simple ulcers in specialized DFU centers.²⁵

In addition, with standard care, only 33% of DFUs will heal despite an organized approach to diagnosis and treatment.²⁶ Twenty to 25% of all hospital admission days for patients with DM are related to foot complications.^{6,27} American statistics in 2006 estimate that 65,700 nontraumatic lower limb amputations were performed in patients with DM, a number that continues to rise.⁵ There is evidence that some measures can prevent DFUs and save nontraumatic amputations. Interprofessional teams are needed to provide detailed and early patient assessment, aggressive treatment, and education. There is substantial economic and clinical benefit to an organized approach for the high-risk patients.²⁸ The risk of lower extremity amputation in the diabetic population is 15 to 46 times higher than their nondiabetic counterparts.^{27,29,30} After an initial amputation, the risk of the contralateral extremity amputation ranges between 9% and 17% in the first year, increasing to 25% to 68% within 3 to 5 years.^{2,27,29,30}

Several studies have found a 41% to 70% decrease in the 5-year survival rate after a lower extremity amputation.^{2,31,32} Iversen et al³³ also reported a 50% higher risk of mortality for patients with DM with a history of DFUs compared to a diabetic population without DFUs.³³

The following list emphasizes the economic burden of DFUs^{34,35} in the United States:

- Increased cost associated with the severity of DFU, with higher-grade DFUs (according to the Meggitt-Wagner classification [Table I]) having more costly disease
- Persons with DM and foot complications had Medicare claims that were 3 times higher than the general population (\$15,309 vs \$5,226 between 1995 and 1996)³⁶
- Healing costs after an amputation averaged \$44,790; healing without amputation averaged \$6,664³⁷
- Access to limb-preserving interventions is suboptimal, leading to an increased amputation rate especially among nonwhite, low-income populations on Medicare/Medicaid compared to individuals with higher economic status and private insurance (extracted data between 1998 and 2002)³⁸

Table I. Diabetic foot ulcer cost as determined by the Meggitt–Wagner classification³⁷

Wagner grade	Retrospective cost analysis per ulcer (average)
1 or 2	\$1,929
3	\$3,980
4 or 5	\$15,792

Table II. Projected annual cost benefits and amputation reduction with interventions for high-risk persons with diabetes^{70,71}

	Potential savings	Amputation reduction
Detailed educational intervention	\$1.1 million	72%
Multiprofessional team approach to diabetes mellitus care	\$750,000	47%
Therapeutic footwear	\$850,000	53%

The Pan American Health Organization (PAHO) reported 3 key cost-saving health service interventions needed to fight noncommunicable disease in the Americas³⁹: educating diabetic patients on recognizing and treating minor foot injuries, the use of appropriate footwear, and accessing knowledgeable health care personnel. Narayan et al⁴⁰ outlined that for developing countries, the highest priorities that could also be cost savings to health care systems included foot care if high risk, glycated hemoglobin (HbA1c) <0.09, or blood pressure <160/95 mm Hg. However, in the Western world, tight control with a target for HbA1c <0.07 and blood pressure <130/85 mm Hg are suggested. The annual projected benefits per intervention for individuals with high-risk DM are shown in Table II.⁴¹

Pathophysiology of the diabetic foot

Several biochemical abnormalities may accelerate neuropathy and vascular foot changes, including hyperglycemia that inhibits the production and activation of endothelial nitric oxide synthase and the reaction of protein with sugars (Maillard reaction) that is linked to diabetic complications and aging. DFUs are caused by neuropathy, ischemia, or both.

The pathophysiology of DFUs requires an appreciation of the role of several contributory factors, including peripheral neuropathy, vascular disease (arterial circulation), and inflammatory cytokines and susceptibility to infection.

Neuropathy. Persons with DM are susceptible to peripheral neuropathy with sensory, autonomic, and motor components. There are several proposed

mechanisms associated with this neuropathy, including nitric oxide blocking and the Maillard reaction between sugars and amino acids (Fig 1).

Nitric oxide blocking. Hyperglycemia, dyslipidemia, insulin resistance, and oxidative stress can lead to cellular damage, endothelial dysfunction, and various diabetes-associated complications through a number of pathways. Hyperglycemia inhibits the production of nitric oxide by blocking endothelial nitric oxide synthase activation, which can lead to higher levels of reactive oxygen species, particularly superoxide. Superoxide is then converted enzymatically to hydrogen peroxide by superoxide dismutases. In the presence of ferrous or cuprous ions, hydrogen peroxide is converted to the highly reactive and damaging hydroxyl radical. In addition, the superoxide anion also binds to nitric oxide (a potent vasodilator), producing peroxynitrite and thereby limiting the bioavailability of a potent endothelium-derived vasodilator. The peroxynitrite anion has a role in the oxidation of sulphydryl groups in proteins, lipid peroxidation, the generation of reactive aldehydes/nitrogen oxides, and the production of proatherogenic low density lipoproteins. The disruption of the endothelium-regulated vascular function not only affects the vasoconstriction response but also causes platelet aggregation, abnormal intimal growth, inflammation, and atherosclerosis formation.³⁷⁻³⁹ Glucoxidation and lipoxidation of vascular wall structural proteins might facilitate atherogenesis through the effect on vessel wall characteristics and the interaction of inflammatory cytokines. This atherogenesis of the small vessels supplying the peripheral nerves contributes to the neuropathy.

Maillard reaction. The Maillard reaction is a slow but complex reaction between reducing sugars and amino groups of biomolecules leading to the production of a complex structures known as advanced glycation endproducts (AGEs).^{40,42,43} This reaction has been hypothesized to be an important mechanism in the pathophysiology of diabetes complications. It has been linked to protein modifications found during aging and diabetes.⁴³ AGE-modified proteins and lipoproteins have roles in the pathogenesis of atherosclerosis.

Excess glucose is converted to sorbital by aldose reductase through the polyol metabolic pathway that consumes nicotinamide adenine dinucleotide phosphate (NADPH).⁴¹ NADPH is further reduced by the activation of the hexosamine biosynthetic pathway that limits the conversion of nicotinamide adenine dinucleotide to NADPH by inhibiting the enzymatic activity of glucose-6-phosphate

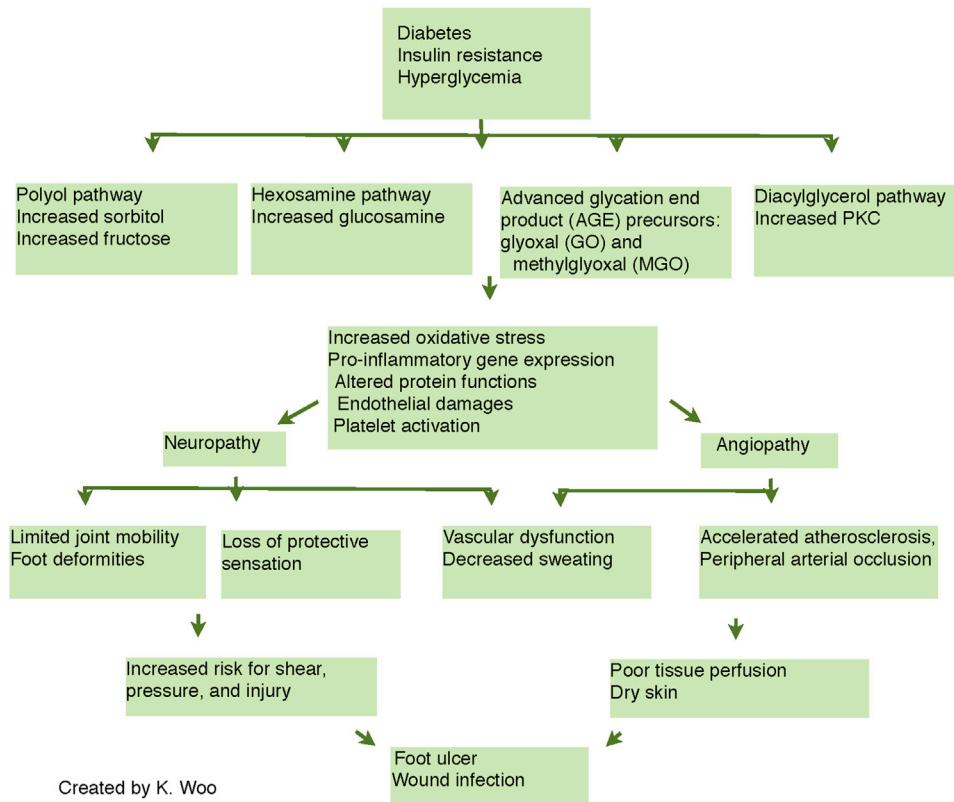


Fig 1. Pathophysiology of diabetic foot ulcers.

dehydrogenase.⁴² The end result is the depletion of NADPH that in turn affects the normal synthesis of key antioxidants, such as glutathione. Decreased antioxidant and increased production of reactive oxygen species play a crucial mediatory role in the pathogenesis and progression of complications in diabetes.

Neuropathy leads to foot deformity or limited joint mobility, resulting in abnormal foot pressure and subsequent callus formation over pressure points (Fig 2). The callus further increases the local pressure and when combined with undetected repetitive injury leads to local tissue injury, inflammation, tissue death (necrosis), and finally ulceration⁴⁴ (Fig 3).

Neuropathy is one of the main contributory factors in the pathogenesis of DFUs. In the absence of neuropathy, pain limits the repetitive injury needed for a full-thickness ulcer to develop.

Diabetic neuropathy can affect the production of neuropeptides, such as nerve growth factor, substance P, and calcitonin gene-related peptide.⁴⁵ Neuropeptides are relevant to wound healing because they promote cell chemotaxis, prompt growth factor production, and stimulate the proliferation of cells. In addition, sensory nerves play a role in modulating immune defense



Fig 2. Diabetic neuropathic feet. Callus formation as a presentation of neuropathy.

mechanisms, with denervated skin showing reduced leukocyte infiltration.⁴⁶ For example, the rate of wound healing in 1-cm excisional wounds on rats created with denervated skin flaps was significantly reduced compared with control wounds.⁴⁷ Immunohistochemical studies identified significantly reduced monocyte, macrophage, and



Fig 3. Diabetic neuropathic foot ulcers overlying the metatarsal head.

T-lymphocyte counts in the denervated wounds. Capsaicin injections induced sensory denervation in rats has been associated with delayed reepithelialization and wound healing.⁴⁸ Murray et al⁴⁹ indicated an 11-fold higher risk of developing ulcers in the presence of callus.

Vascular disease. Micro- and macrovascular disease in persons with DM may impair healing of the ulcers and is critically important. Ischemia has been reported as a contributing factor in 90% of diabetic patients undergoing major amputation.^{50,51} Prolonged inflammatory response within the microcirculation can lead to thickening of capillary basement membranes with arteriolar hyalinization, compromising the normal movements of nutrients and activated leukocytes between the capillary lumen and the interstitium. The relatively inelastic capillary walls may explain the limited capacity for vasodilatation in response to local injury, leading to functional ischemia.

Inflammatory cytokines and susceptibility to infection. Once an ulcer develops, susceptibility to infection exists because of a loss of innate barrier function. In chronic wounds, microorganisms aggregate together and grow within communities where they encase themselves within extracellular polymeric substances containing polysaccharides and lipids. This encased collection of microorganisms, known as a biofilm, increases resistance to antimicrobial, immunologic, and chemical attacks.⁵² Bacterial biofilms contribute to a delay in healing

and the occurrence of chronic inflammation and recurrent infections with the intermittent release of single (planktonic) organisms.⁵²

DM also affects normal leukocyte function and immune functions, decreasing host resistance and rendering this patient population more susceptible to superficial increased bacterial burden in the wound base and deep or surrounding skin infection.^{53,54} For example, Mowat et al⁵⁵ documented an in vitro leukocyte chemotaxis defect in persons with diabetes. Phagocytosis and bactericidal capacity was significantly reduced in the presence of hyperglycemia.⁵⁵ Once DFUs have formed, they are often slow to heal because of impaired cell migration.⁴³ Stojadinovic et al⁵⁶ identified that overexpression of c-Myc and β -catenin at the edge of chronic DFUs may lead to impairment of keratinocyte migration and inhibition of healing in DFUs. A number of wound fluid studies have identified an elevated level of matrix metalloproteinases in the exudate associated with DFUs. These elevated levels may result in sustained inflammation with a net destruction of the collagen matrix required for healing.

INCREASED PLANTAR PRESSURE AND ITS CONSEQUENCES

Key points

- All patients with DM should undergo a thorough examination with both shoes and socks off
- The presence of callus is associated with an increase in local pressure because of the loss of protective sensation associated with neuropathy. It is of utmost importance to remove the callus at regular intervals (ideally at every visit) to prevent pressure ulcers
- A blister may be the result of friction and shear (movement between the foot and the shoe, orthotic, or special device)
- Deformities and limited range of motion of the foot and ankle joints can alter foot mechanics and cause critical pressure and ulceration

Once an ulcer develops, there are different techniques that can be used to deflect increased plantar pressure, including a total contact cast, a removable cast walker, half shoes, and custom orthotics. However, before ulcer development, it is necessary that all patients with DM and potential diabetic foot changes should have a thorough examination with the removal of both the patient's shoes and socks. The presence of callus is

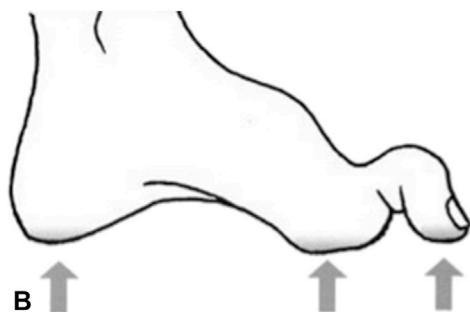


Fig 4. A and B, Claw toes. Dorsiflexion of the proximal phalanx on the lesser metatarsophalangeal joint combined with flexion of both the proximal and distal interphalangeal joints that cause pressure. Claw toe can affect the second, third, fourth, or fifth toes.

associated with an increase in local pressure. Motor neuropathy causes unequal muscle pull. The plantar muscles are affected first; the loss of distal innervation creates unequal pull from the proximal muscles on the dorsal surface of the foot. This pressure differential results in a “cocked up” toe, but unequal pressure can cause additional deformities, such as claw toes (dorsiflexion of the proximal phalanx on the lesser metatarsophalangeal joint, combined with flexion of both the proximal and distal interphalangeal joints; Fig 4).^{57,58} The claw toe is distinguished from the hammertoe, which has a deformity of proximal metacarpophalangeal joint and interphalangeal joint of the toe, causing consistent flexure like a hammer (Fig 5).⁵⁸ The deformity results in prominent plantar surface metatarsal heads and clawed toes. These deformities are often associated with skin breakdown on the doral or plantar surface of the forefoot from poorly fitting shoes with an inadequately sized toe box. As the metatarsal heads drop, the corresponding fat pads herniate distally under the base of the toes. The pressure from the collapsed bone close to the plantar surface results in local callus formation over the metatarsal heads. These changes can be recognized by a thorough examination of the base of the toes with the metatarsal heads becoming easily palpated just below the plantar surface. Callus is associated with increased risk of ulceration.

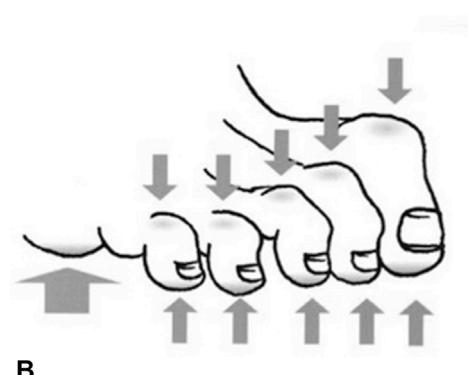


Fig 5. A and B, Hammer toes. Note the deformity of the proximal metatarsophalangeal and interphalangeal joints of the toes, causing consistent flexure like a hammer.

A blister may be the result of friction and shear (movement between the plantar surface of the foot and the sole of the shoe), and this is also a potential break in the skin barrier, leading to an increased risk of infection. Bunions caused by hallux valgus are important foot deformities associated with a wide forefoot and an additional risk site at the sides of the foot for ulcer formation.

Glycosylation of collagen by hyperglycemia leads to stiffness of connective tissues (ie, joint capsules and ligaments). This impairs joint function and results in restricted range of motion.⁵⁹ An example is the equinus deformity, with restriction of dorsiflexion of the ankle joint often associated with fixed toes, leading to critical plantar pressure in the forefoot and toe area. Patients may be referred for ankle tendon lengthening to correct this deformity or, in some cases, to promote the healing of persistent forefoot plantar ulcers.

Evaluation of the risk factors and risk stratification is an important guide for prognosis and diabetic foot care. The International Working Group on the Diabetic Foot (IWGDF) risk categorization tool is a useful system to classify these patients (Table III).^{60,61}

Table III. The International Working Group on the Diabetic Foot risk categorization tool

Category	Risk factor	Ulcer incidence	Amputation incidence	Prevention and treatment
0	No sensory neuropathy	2-6%	0	Reevaluation once a year
1	Sensory neuropathy	6-9%	0	Podiatry/chiropody every 6 months; over the counter shoes and insoles
2	Sensory neuropathy and foot deformity or peripheral vascular disease	8-17%	1-3%	Podiatry/chiropody every 2-3 months; therapeutic shoes and insoles; patient education
3	Previous ulcer or amputation	26-78%	10-18%	Podiatry/chiropody every 1-2 months; therapeutic shoes and insoles; patient education

Derived from Johnson et al⁵⁸ and Birke et al.⁵⁹

WHY USE A SCREENING TEST?

Key points

- Identification of the high-risk foot is an essential component of diabetes care
- A simplified screening can detect the high-risk foot
- An interprofessional approach can reduce the amputation rate by 40% to 85%
- Neuropathy, peripheral arterial disease, and a previous foot ulcer or amputations are major risk factors for developing a foot ulcer

The high-risk diabetic foot can be identified with simplified screening tests, and subsequent foot ulcers may be prevented.⁶² One recently developed and validated test is a simplified 60-second screening test (video available at www.Woundpedia.com or www.diabeticfootscreen.com; Fig 6).⁶² Referral to a foot specialist may prevent ulceration and possibly decrease the risk of lower extremity amputation.

Many specialists, including dermatologists, frequently encounter patients with DM, and there is the opportunity to screen these patients when they are in the office for a routine visit. In fact, dermatologists are more likely to survey a patient's skin than any other specialist and may have a special opportunity to identify at-risk patients or early DFUs. Overall, this screen can identify a large percentage of persons with DMs at high risk of foot ulceration and subsequent preventable lower limb amputation.^{37,63-65} Several studies have shown that amputation could be reduced by 40% to 85% through the detection of high-risk patients and a subsequent interprofessional approach that focuses on preventive measures.⁶⁶⁻⁶⁸

Screening may also detect foot ulcers and other lesions that the patient is not aware of, including blisters, calluses, fissures, tinea pedis, and ingrown toenails.^{62,67}

Previous studies of persons with DM have identified neuropathy, peripheral arterial disease (PAD), a previous foot ulcer, or previous amputation as risk factors for developing a foot ulcer.^{14,69} Lavery et al⁶¹ and Peters et al,⁶⁹ as part of the IWGDF, identified the yearly incidence ulceration rate. If a person has DM and no other complication, such as neuropathy or PAD, they have a 2% risk of developing a foot ulcer. With neuropathy, the incidence increases to 4.5% and with additional PAD to 13.8% annually. The incidence of foot ulceration is increased 32.2% with any 2 of the following criteria: previous foot ulcer, previous amputation, PAD, and neuropathy.^{61,69}

Identification of the high-risk foot is an essential component of diabetes care. It focuses attention and provides a means to direct limited resources to those patients most at risk of developing a DFU. The approach to the cutaneous changes associated with DM can be optimized when professionals work toward a standardized plan.

CLINICAL PRESENTATIONS

The presence of a DFU is a consequence of multiple factors and is not usually the result of a single pathology.

Neuropathy

Key points

- Increased plantar pressure resulting from neuropathy is the major risk factor for diabetic foot ulcers
- Diabetic neuropathy has 3 components: sensory, autonomic, and motor neuropathy
- Loss of protective sensation can be measured with a 10-g monofilament (the Semmes-Weinstein monofilament test)
- Autonomic neuropathy causes dryness of the skin, and motor neuropathy results in a claw

Screening for the high risk diabetic foot: A 60-Second Tool (2012) © Sibbald					
Name: _____ ID#: _____ Phone #: _____ Facility: _____ DOB (dd/mm/yy): _____ / _____ / _____ Gender: M <input type="checkbox"/> F <input type="checkbox"/> Years with diabetes: _____ Ethnicity: Black <input type="checkbox"/> Asian <input type="checkbox"/> Caucasian <input type="checkbox"/> Mixed <input type="checkbox"/> Other <input type="checkbox"/> Date of Exam (dd/mm/yy): _____ / _____ / _____		CHECK BOTH FEET (Circle correct response) "YES" on either foot = HIGH RISK			
		LEFT	RIGHT		
HISTORY	1. Previous ulcer	NO	YES	NO	YES
	2. Previous amputation	NO	YES	NO	YES
PHYSICAL EXAM	3. Deformity	NO	YES	NO	YES
	4. Absent pedal pulses (Dorsalis Pedis and/ or Posterior Tibial)	NO	YES	NO	YES
FOOT LESIONS <i>Remember to check 4th and 5th web spaces/nails for fungal infection and check for inappropriate footwear.</i>	5. Active ulcer	NO	YES	NO	YES
	6. Ingrown toenail	NO	YES	NO	YES
	7. Calluses (thick plantar skin)	NO	YES	NO	YES
	8. Blisters	NO	YES	NO	YES
	9. Fissure (linear crack)	NO	YES	NO	YES
	10. Monofilament exam (record negative reaction): a) Right _____ /10 negatives (≥ 4 negatives = Yes)	NO	YES	NO	YES
	b) Left _____ /10 negatives (≥ 4 negatives = Yes)	Total # of YES: _____		Total # of YES: _____	
PLAN					
a) POSITIVE SCREEN- Results when there are one or more "Yes" responses. Refer to a foot specialist or team for prevention, treatment and follow up. (Bony deformity, current ulcer, absent pulse are most urgent). These individuals are at increased risk of a foot ulcer and/or infection. Patients should be educated on what changes to observe and report, while waiting for the specialist appointment. Referral to: _____ Appointment time: _____					
b) NEGATIVE SCREEN- Results when there are all "No" responses. No referral required. Educate patient to report any new changes to their healthcare provider and re-examine in 1 year. One Year Date for Re-Examination (dd/mm/yy): _____ / _____ / _____					
Completed By: _____ Date: _____					
Additional Note: See reverse side for recommendations from the <i>International Diabetes Federation, & International Working Group on the Diabetic Foot</i> . Local referral patterns may vary depending on expertise and available resources.					

Fig 6. The 60-second screening tool. *Continued on next page.*

toe deformity, loss of reflexes, and muscle atrophy

- Diabetic sensorimotor polyneuropathy will develop within 10 years of the onset of diabetes mellitus in 40% to 50% of patients**

Neuropathy is a major predictor for ulceration.⁶⁹ The neuropathic foot does not ulcerate spontaneously, but ulcer formation is a combination of neuropathy and other factors, such as repetitive unperceived trauma from excessive ambulation, poorly fitting shoes, walking in stockings without

shoes, or walking barefoot, along with callus formation over areas of increased pressure.

The 3 main mechanisms of injury are as follows²⁷: (1) footwear (ill-fitting shoes resulting in low but prolonged pressure); (2) weight-bearing (repetitive moderate pressure and friction or shear forces that result in blister formation); and (3) trauma (including penetrating injury, meaning high pressure with a single or repetitive exposure of direct pressure).

The biomechanics of the foot are altered such that the claw toe results in the metatarsal heads moving close to the skin surface and the fat pads herniate

Screening for the high risk diabetic foot: A 60-Second Tool (2012) © Sibbald

General Instructions:

This diabetic foot screening tool is designed to identify individuals with high-risk diabetic feet. This screening tool is a simplified 60-second assessment for each foot to be implemented by any healthcare provider. Preparation involves having a 5.07g monofilament available and asking patient to remove their shoes and socks.

Normal screening findings are indicated as "No" (not requiring referral) and abnormal screening findings are indicated as "Yes" (requiring referral). Generation of a list of local reputable foot specialists and/or teams for referring is recommended.

Screening involves:

- Inform patient about the simplified 60-second screening and explain the reason for the examination.
- Fill in patient's demographic data in top left section of screening tool.
- Assess both feet. Circle either a "Yes" or "No" response for questions 1-10.
- Any "Yes" response requires follow up or a referral to a foot specialist and/or team.

Question	"Yes" Response
1	"Yes", if previous ulcer from history is observed: Ask the patient and assess both lower legs and feet for the presence of a healed ulcer as evidenced by scar tissue.
2	"Yes", if previous amputation of digit(s), foot or limb is observed.
3	"Yes", if deformity and/or abnormality in shape or structure of either foot is observed (bony prominences/hammer toes).
4	"Yes", if absent pedal pulses (palpate Dorsalis Pedis and if absent check Posterior Tibial). A yes answer requires absence of both pulses.
5	"Yes", if active ulcer(s) present: Openings in the skin with a dermal or deeper base.
6	"Yes", if ingrown toenail present. Inspect distal corners for embedded nail and/or thickened nail fold skin.
7	"Yes", if callus present (thick plantar skin): Assess and inspect for presence of thick areas of keratin on the bottom or sides of feet and toes.
8	"Yes", if blister(s) present: Observe for fluid (serum, blood or pus) under intact skin surface.
9	"Yes", if fissure (linear crack). Observe for a linear break with dermal base or deeper base.
10	"Yes", if Monofilament Exam identified 4 or more negative reactions (lack of feeling): Follow the monofilament exam instructions below. Each foot is examined separately.

**Steps for Monofilament Test for Neuropathy:**

- Show and touch monofilament to patient's arm or upper leg.
- Ask the patient to close their eyes and say yes when they feel the monofilament.
- Touch monofilament until filament bends in a letter "c" shape, assessing all 10 areas on diagram (Do not test over calluses, scars or ulcers)
- Lack of feeling (4 or more out of 10) - indicates a negative reaction = Neuropathy = "YES" on screening tool

Foot Risk Classification and Follow-up Guide						
Assessment Findings ↓	RISK	Follow Up (mths)	Prof. Nail Care	Orthopaedic Shoes	Orthotics + Diabetic Socks	Activity
No Neuropathy	0	12	-	Well fitting	Well fitting shoes	As able
Neuropathy	1	6	+/-	Professional fit	Custom full contact	As able, monitor, guided by foot exam
Deformity	2a	3-4	+/-	+/- custom fit	Custom full contact	Avoid excessive walking, ✓ non-impact exercises
Peripheral Vascular Disease	2b	3-4	+	Professional fit	Soft full contact	Dependent on ischemic pain, ✓ non-impact exercises, or as recommended by vascular team consult
Ulcer Hx or Active ulcer	3a	1-2	+	Professional fit	Custom fitted	Activity dependant on exam, ✓ non-impact exercises
Hx Amputation	3b	1-2	+	Special clinic (assessment) Modified footwear	Specialized clinic: amputation prostheses, +/- walking aid	Based on tissue tolerance, ✓ non-impact exercises

Modified from International Diabetes Federation, International Working Group on the Diabetic Foot, 2008

Fig 6. Continued.

upward, obliterating the space just below the toe webs.

The resulting increased trauma from pressure associated with calluses or friction/shear-associated blisters (ie, vesicles, bullae, and hemorrhagic bullae) leads to subsequent tissue injury. Sensory neuropathy contributes to the lack of perceived tissue injury (loss of protective sensation).^{26,70,71} Diabetic sensorimotor polyneuropathy will develop sooner with poor glycemic control, but often within 10 years of the onset of diabetes in 40% to 50% of patients with type 1 or type 2 DM.^{72,73}

The onset of diabetic neuropathy is insidious, and many patients are unaware of the process. Although neuropathy is associated with a loss of protective sensation, neuropathic pain may decrease quality of life. This pain may present spontaneously as burning, stabbing, shooting, stinging, hyperesthesia, or even allodynia (an increased response to normal stimuli, such as light touch). This represents sensory neuropathy, which is 1 of the 3 components of neuropathy represented by the mnemonic SAM (sensory, autonomic, and motor).

A thorough physical examination, including the removal of shoes and socks, is a more reliable tool to

detect neuropathy than patient history. The physical examination may reveal the characteristic claw toe, dry skin, and a loss of reflexes. The test for neuropathy is with the 10-g (5.07) Semmes–Weinstein monofilament^{34,71} and a 128-Hz tuning fork for perception of vibration sensory stimuli. The monofilament test is a simple bedside screening test that has been widely used in clinical practice. The inability to feel a 10-g (5.07) monofilament is a sensitive predictor for neuropathy and ulceration.⁷⁴ With their eyes closed, the patient is asked if they feel the monofilament while the monofilament is placed against the intact skin (with no callus) and allowed to buckle.⁷⁵ Most authors suggest testing 10 sites; the absence of sensation in 3 to 4 sites is consistent with a loss of protective sensation.⁷⁶ Other techniques exist to detect sensory neuropathy, including a simple prototype robotic monofilament inspector that has been used to diagnose neuropathy.⁷⁷

Neuropathy impairs the ability to perceive injury because of a loss of protective sensation. Autonomic neuropathy involves the sympathetic nervous system and presents as anhidrosis with dry skin and fissures that needs to be distinguished from other causes of dry plantar skin. These changes must be distinguished from fungal infection, because the fourth and fifth web spaces are common areas for fungal intertrigo while the plantar surface and the sides of the foot are common areas for a moccasin distribution. The nail changes include distal streaking or more complete nail plate asymmetric nail changes of fungal infections. Any patient with a suspicion of fungal infection should have a potassium hydroxide microscopic examination and/or fungal culture to confirm the diagnosis. Because of the increased risk for complications of bacterial infection, the presence of superficial fungal infection in patients with DM may lead to a greater risk for associated bacterial infections.

Motor neuropathy can be detected with a loss of ankle reflexes.^{24,78} Motor neuropathy is tested with ankle reflex, and a loss of reflexes is associated with deformity, wasting of intrinsic muscles, and muscle imbalance with cocked up toes.

Education for persons with DM regarding proper foot care may help prevent DFU and amputations, especially for those who are at high risk.^{79,80}

PERIPHERAL VASCULAR DISEASE

Key points

- Diabetic foot ulcers can be divided into neuropathic, ischemic, and neuroischemic foot ulcers, with the latter 2 having a less favorable prognosis

- Assessment of the vascular status requires a thorough history and physical examination; however, definitive diagnoses require more advanced, technical examinations
- A palpable pulse in the foot indicates a pressure of at least 80 mm Hg; however, a palpable pulse, especially in diabetes mellitus (because of medial sclerosis) does not exclude poor perfusion
- Segmental continuous wave Doppler examination and ideally toe pressure measurement of the large toe (toe–brachial pressure index) are regarded as the criterion standard for the evaluation of limb perfusion in persons with diabetes mellitus
- Duplex ultrasonography may aid in the morphologic diagnosis of occlusions and planning of interventions
- Transcutaneous oxygen tension measurement may be of important value, especially in patients with diabetic foot ulcers, because it reflects oxygen supply to the end organ (the skin) by macro- and microcirculation
- Ischemic disease increases the risk for limb loss. If vascular (ischemic) signs and symptoms are present, refer immediately to a vascular surgeon for proper testing and possible revascularization

PAD is another important contributory factor in DFUs. In some populations, PAD is present in >50% of patients with DFUs.^{81,82} DFUs can be divided into 3 main categories: diabetic neuropathic, diabetic ischemic, and diabetic neuroischemic foot ulcers (Table IV).^{41,42} This ischemia represents macrovascular disease. Individuals with ischemic and neuroischemic foot ulcers have a poorer prognosis, and vascular procedures are often warranted.^{83–88} Friction and trauma in an ischemic foot can cause skin breakdown, especially when complicated by infection (Fig 7).

The assessment of vascular status requires a thorough history and physical examination, including any history of previous PAD, intermittent claudication, or rest pain (in persons with DM, often not present because of neuropathy). Examination for clinical signs should include the following: inspection for pallor, dependent rubor, decreased skin temperature, hair loss, atrophic shiny skin, and palpation of the dorsalis pedis or posterior tibial pulses. Although the physical examination provides important qualitative information, the sensitivity of the clinical tests is limited. The absence of the dorsalis pedis pulse has a sensitivity of 50%, a specificity of 73.1%, and a low positive

Table IV. Comparison of 3 major groups of foot ulcers (neuropathic, ischemic, and neuroischemic)

Ulcer characteristics	Neuropathic	Ischemic	Neuroischemic
Common location	Plantar	Plantar and/or dorsal aspect of toes and foot	Plantar and/or dorsal aspect of toes and foot
Morphology	Surrounding callus	Punched out, black eschar	Necrosis and callus
Pain	Mild	Severe	Dull pain
Type of pain	Neuropathic; sharp, stabbing, or burning	Nociceptive and claudication; dull pain or persistent sharp pain	Combination of both
Callus	+++	—	++(+)
Bone deformity	+++	—	++(+)
Pulses	Present	Weak or absent	Weak or absent
Skin temperature	Warm	Cool	Cool
Surrounding skin	Loss of sensation, callus	Pallor, shiny, rubor, or pale; cool	Both

predictive value of 17.7%.⁸⁹ In 8% of healthy individuals, the dorsalis pedis is absent; the tibialis posterior pulse is absent in 3% of cases.^{90,91} A palpable pulse in the foot represents the presence of at least 80 mm Hg pressure.⁹² However, a palpable pulse does not rule out PAD, especially in diabetic patients suffering from medial calcinosis (abnormal deposition of calcium of the vessel wall).⁹³ Generally, significant arterial disease is most often excluded when the dorsalis pedis or posterior tibial pulses are clearly palpable. The more accurate technical tests to rule out PAD include qualitative segmental Doppler waveforms or quantitative ankle–brachial pressure index (ABPI) assessment, provided that the vessels are compressible and the ABPI is <1.4 or >0.8.

In a recent article by Faglia et al,⁹⁴ the ankle pressure could not be measured in 109 (41.8%) patients because of occlusion of both tibial arteries in 75 (28.7%) patients or because of the presence of arterial calcification in 34 (13.0%) patients.⁹⁵ In diabetic patients, the toe–brachial pressure index (TBPI) is the screening test of choice rather than ABPI because of the common occurrence of medial calcinosis. However, in a recent study, it has been shown that because of a lesion on the great toe and/or lesions the midfoot, 187 of 261 patients (71.6%) could not be examined properly by either the ABPI or the TBPI.⁸⁸ Therefore, color-coded Duplex ultrasonography represents the criterion standard of noninvasive vascular assessment once relevant PAD is suspected and/or simple examination is not possible.

Because of the presence of arteriovenous shunting, an ischemic foot might appear pink and even warm in the presence of impaired perfusion. There may be a localized arterial block; angiosomal defects should be referred to a vascular surgeon. Angiography can verify the real anatomic correlates

for nonhealing ulcers and assist in planning the best intervention.^{84–87} The foot can be divided into 6 anatomic regions corresponding to the 6 proposed angiosomes.^{75,76,84,87} A distinct source artery feeds each angiosome.⁸⁴ Wounds may fail to heal because of inadequate local vascular supply despite having palpable pulses. Early referral to a vascular surgeon or specialist is recommended for targeted primary angioplasty following this angiosomal model and can therefore improve clinical success.^{86,87}

Skin perfusion pressure is a good indicator of lower extremity microcirculation.⁹⁶ Transcutaneous oxygen tension reflects the amount of oxygen that has diffused from the capillaries through the epidermis to an electrode at the measuring site. It provides instant, continuous information about the body's ability to deliver oxygen to the tissue. This test is usually conducted in a vascular laboratory and has recently been shown to be an indicator for critical limb ischemia (CLI).⁸⁸ Faglia et al⁸⁸ concluded that if diabetic patients presented with rest pain and/or foot lesions, it is essential to measure the foot oxygen tension for the diagnosis of CLI, and that this was true not only when arterial pressure was not measurable but also when arterial pressure was ≥ 70 mm Hg.

CHARCOT FOOT

Key points

- **Diabetes mellitus is the most common cause of Charcot deformity in the Western world**
- **Charcot foot may present with redness, swelling, deformity, and increased foot temperature**
- **In the acute phase, differentiating Charcot disease from cellulitis and the chronic phase of osteomyelitis may be difficult**
- **Non-weight-bearing and immobilization is the key treatment choice in the acute stage**



Fig 7. Diabetic neuroischemic foot. Minor trauma from footwear led to gangrene of the fifth toe and tissue loss on the laterodorsal surface of the foot. Without rapid arterial revascularization, progression of gangrene and infection will usually occur, resulting in below the knee amputation or sepsis.



Fig 8. Charcot foot.

Charcot foot is a late complication of peripheral motor neuropathy of any cause. Charcot foot results from repetitive trauma to insensitive bones and joints of the foot (Fig 8). DM is the most common cause of Charcot deformity in the Western world and should be considered in any patient who presents with a warm swollen foot, even in the absence of ulceration. A diagnosis of osteomyelitis is more likely if there is ulceration, although both Charcot foot and osteomyelitis can exist simultaneously.^{97,98} Dislocation of bones and joints without a preceding known trauma is the characteristic of Charcot foot caused by long-standing diabetic neuropathy.⁹⁹ Charcot foot may present as redness, swelling, deformity, increased foot temperature, and ulceration (Fig 9). In the acute phase of Charcot disease, differentiating it from cellulitis and



Fig 9. Charcot foot. Note the typical “rocker bottom deformity,” with an ulcer at the area of maximal pressure of the foot because of the loss of arch integrity.

osteomyelitis is difficult. Chronic osteomyelitis usually has an insidious presentation and is refractory to treatment. The acute radiographic changes of osteomyelitis include focal osteopenia and lucency in the cortex or medullary bone, while chronic changes may lead to the sequestration of dead bone.⁷⁷ The differentiation of osteomyelitis from osteopathy is difficult. The radiographic changes of chronic osteopathy include fractures, bone destruction, and periosteal new bone formation.⁷⁷ In the chronic phase of Charcot foot, deformity is more predominant. The exact pathogenesis remains to be determined. Multiple recurrent stress fractures develop because of osteopenia. The expression of a polypeptide cytokine (a specific receptor activator of a nuclear factor- $\kappa\beta$ ligand [RANKL]) has been described as a possible mechanism for osteopenia and neuropathy.⁹⁹⁻¹⁰¹ Inflammation mediated by the release of proinflammatory cytokines also increases osteolysis.

The healing process may last more than 6 to 9 months, during which the foot (without off-loading and immobilization) usually becomes distorted and turns into a “clinically visible” Charcot foot. The resultant fixed deformity may include a rocker bottom foot. The clinician should examine the foot for abnormal contours and compare both feet to monitor any differences in the bony contours. The changes can be present in the forefoot, midfoot, hind foot, or heel area as well as the ankle. Chronically, these deformities lead to an increased susceptibility to ulceration.

A high index of suspicion and early diagnosis with appropriate diagnostics can play a key role in management. A radiograph of the foot may be useful, and the most commonly affected joints are in the midfoot region (ie, the cuneiform/metatarsal area). A swollen foot with increased temperature and no ulcer in a patient with DM is most likely a Charcot foot, but if there is an ulcer present, osteomyelitis is more likely. Occasionally, both conditions coexist.

A bone scan reveals increased blood flow and bone intake. In limited cases, magnetic resonance imaging or white cell scans aid in the differentiation from osteomyelitis. Careful weight-bearing limitation is imperative to stop the cycle of structural damage and inflammation. Management includes using a total contact cast, potential medical treatment with bisphosphonates, and surgical management of resultant deformity once the foot has been stabilized.¹⁰²

Differential diagnosis

Although the vast majority of DFUs in diabetic patients are caused by neuropathy, the differential diagnosis includes traumatic ulcers, inflammatory ulcers (vasculitis/ pyoderma gangrenosum), vasculopathies, and malignancies. In 2 studies by Kong et al,^{103,104} 7 cases of melanoma presenting as foot ulcers have been reported. Acral melanoma is frequently misdiagnosed and commonly presents with amelanotic and ulcerated lesions.¹⁰⁵ Skin biopsy specimens will be diagnostic. Nonmelanoma skin cancers (Fig 10) and metastatic lesions may present as DFUs in patients with DM.¹⁰⁶

CLASSIFICATION OF DIABETIC FOOT

ULCERS

Key points

- The Meggitt–Wagner classification is mainly based on the wound depth and presence and location of infection, with grades ranging from 0 to 6
- The University of Texas classification categorizes wounds with 4 grades based on the wound depth, presence of infection, and presence of ischemia

Should an ulcer develop, clinical staging is critical because it portends prognosis. One of the most commonly used classification systems for diabetic foot ulcers is the Meggitt–Wagner classification. The system is primarily based on the wound depth and presence and location of wound infection, with grades ranging from 0 to 6. The first 3 grades (0-2) are based on the depth of the

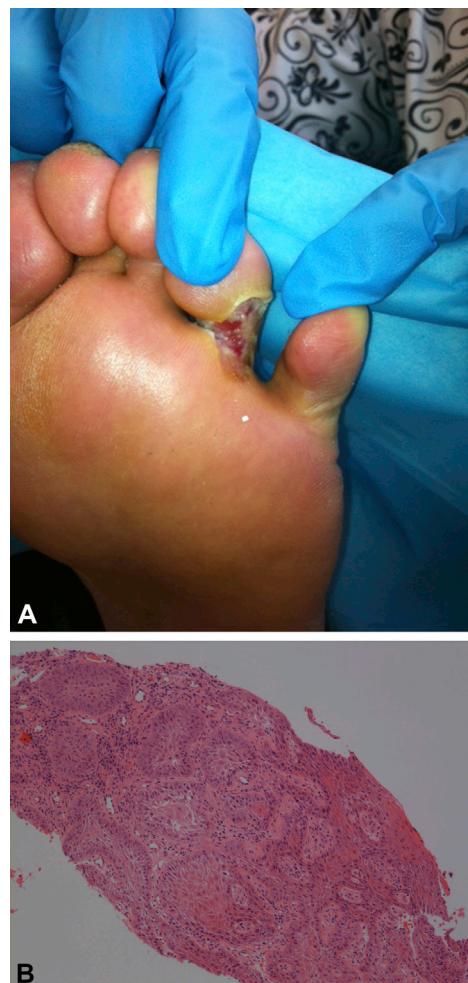


Fig 10. **A**, Squamous cell carcinoma presenting as a foot ulcer in a patient with a long history of diabetes. **B**, Histopathology shows nests of atypical keratinocytes within the dermis. (Hematoxylin-eosin stain; Original magnification: X200.)

lesion through the soft tissue, and the last 3 grades (3-5) are based on the extent of foot infection.¹⁰⁷ The University of Texas wound classification system categorizes wounds into 4 grades (0-III) based on the wound severity. Grade 0 represents a pre- or postulcerative site. Grade I ulcers are superficial, grade II ulcers penetrate to the tendon or joint capsule, and grade III ulcers penetrate the bone or into the joint. With each wound grade, there are 4 stages: nonischemic clean (A), nonischemic infected (B), ischemic wounds (C), and infected ischemic wound (D).^{63,108}

Various classification systems have been proposed for DFUs, with no single universally accepted system. In addition to the staging systems listed above, the IWGDF has developed a classification system for all ulcers according to the 5 categories of perfusion, extent/size, depth/tissue

Table V. Comparison of 3 diabetic foot classifications

Classification		
Meggitt-Wagner	University of Texas	PEDIS (research-oriented)
Grade 0—No ulcer in a high-risk foot	Grade I-A—Noninfected, nonischemic superficial ulceration	Perfusion
Grade 1—Superficial ulcer involving the full skin thickness but not underlying tissues	Grade I-B—Infected, nonischemic superficial ulceration	Extent/size
Grade 2—Deep ulcer, penetrating down to ligaments and muscle, but no bone involvement or abscess formation	Grade I-C—Ischemic, noninfected superficial ulceration	
Grade 3—Deep ulcer with cellulitis or abscess formation, often with osteomyelitis	Grade I-D—Ischemic and infected superficial ulceration	
Grade 4—Localized gangrene	Grade II-A—Noninfected, nonischemic ulcer that penetrates to capsule or bone	Depth/ tissue loss
Grade 5—Extensive gangrene involving the entire foot	Grade II-B—Infected, nonischemic ulcer that penetrates to capsule or bone	Infection
	Grade II-C—Ischemic, noninfected ulcer that penetrates to capsule or bone	
	Grade II-D—Ischemic and infected ulcer that penetrates to capsule or bone	
	Grade III-A—Noninfected, nonischemic ulcer that penetrates to bone or a deep abscess	Sensation
	Grade III-B—Infected, nonischemic ulcer that penetrates to bone or a deep abscess	
	Grade III-C—Ischemic, noninfected ulcer that penetrates to bone or a deep abscess	
	Grade III-D—Ischemic and infected ulcer that penetrates to bone or a deep abscess	

PEDIS, Perfusion, extent/size, depth/tissue loss, infection, and sensation.

loss, infection, and sensation (PEDIS).⁶⁴ Several studies have shown a link between poor outcomes and increased severity of disease (higher stage or grade).⁶³ All 3 classifications are compared in Table V. The University of Texas classification is the classification that is most commonly used in wound care clinics. While classification systems are important and are focused on wound characteristics, the anatomic location of a diabetic neuropathic or ischemic ulcer can also relate to healing potential. Forefoot wounds have a higher chance of healing compared to more proximal wound locations. Specifically, heel region ulcers are associated with higher amputation rates and a greater difficulty in healing.¹⁰⁷

CONCLUSION

Diabetic foot screening should be completed in all diabetic ambulatory care settings (ie, physician offices, diabetic education centers, and home care). PAD, neuropathy, deformity, and previous amputation are the main factors contributing to the development of DFU. Early recognition of the high-risk foot is imperative to decrease morbidity and mortality associated with amputations. An interprofessional approach (ie, physicians, nurses, and foot care specialists) can support patients and their circle of

care. The management of DFUs will be further addressed in part II of this continuing medical education article, where we will review the role of infection, plantar pressure redistribution, debridement, local wound dressings, and advanced (active) therapies.

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Diabetic foot ulcers

Part II. Management

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Learning Objectives

After completing this learning activity, participants should be able to evaluate a person with diabetic foot ulcer with holistic patient assessment (HbA1c) and other metabolic factors; address adequate vascular supply to heal deep and surrounding infection and plantar pressure distribution; identify patient-centered concerns including pain and activities of daily living; assess local wound care; and optimize the use of advanced therapies.

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The management of diabetic foot ulcers can be optimized by using an interdisciplinary team approach addressing the correctable risk factors (ie, poor vascular supply, infection control and treatment, and plantar pressure redistribution) along with optimizing local wound care. Dermatologists can initiate diabetic foot care. The first step is recognizing that a loss of skin integrity (ie, a callus, blister, or ulcer) considerably increases the risk of preventable amputations. A holistic approach to wound assessment is required. Early detection and effective management of these ulcers can reduce complications, including preventable amputations and possible mortality. (*J Am Acad Dermatol* 2014;70:21.e1-24.)

Patients with diabetes mellitus (DM) are prone to multiple complications, including foot ulcers caused by neuropathy and peripheral arterial disease (PAD). While a patient with DM may develop a leg ulcer, this would be more likely caused by venous disease, because DFUs occur on the feet and venous leg ulcers most commonly occur on the leg and only rarely on the dorsal surface of the foot (Fig 1). However, should venous disease coexist or edema of any cause be present, addressing this may facilitate healing. The development of foot ulcers is part of the causal pathway to amputation, because a foot ulcer precedes nontraumatic lower limb amputation in 85% of patients with DM. Therefore, prompt recognition and appropriate interprofessional treatment can prevent unnecessary amputations.^{1,2} Dermatologists should be familiar with identification of the high-risk foot and, if appropriate, the necessary referrals for DFU prevention and treatment.

The effective management of at-risk individuals includes a holistic approach to care, including (1) assessment and optimization of vascular supply

CAPSULE SUMMARY

- Patients with diabetes mellitus have an increased risk of developing diabetic foot ulcers and are at risk for delayed healing that increases the risk of complications.
- Diabetic foot ulcers are classified as neuropathic, ischemic, or neuroischemic, but the presence of concomitant venous disease or other conditions that cause foot edema can also delay healing.
- Treatment includes: optimizing vascular supply, early detection and treatment of deep and surrounding tissue infection, and plantar pressure redistribution.
- Comprehensive evaluation of the patient should be performed in concert with local wound care.
- Radiologic assessments should include a baseline foot radiograph along with appropriate follow-up and a magnetic resonance imaging scan when indicated.
- Key elements of local wound care assessment and treatment include adherence with pressure redistribution (off-loading), surgical debridement of the callus and ulcer surface, and the topical antimicrobial treatment of local infection along with moisture balance.

when possible; (2) early detection and treatment of the infection; and (3) appropriate plantar pressure redistribution. In addition, addressing systemic (metabolic) factors that may delay healing is also helpful.

Among metabolic factors, glucose control likely is of importance.³ A greater elevation in blood glucose level is associated with a higher potential for suppressing the inflammatory response and decreasing the host's response to infection. The best indicator of glucose control over a period of time is glycated hemoglobin (HbA1c) level. This test measures the average blood sugar concentration over the 90-day life span of the average red blood cell in the peripheral circulation. The higher the HbA1c level, the more glycosylation of the hemoglobin in the red blood cell will occur.⁴ Blood glucose levels >11.1 mmol/L (equivalent to >310 mg/mL or a HbA1c level of >12) is associated with decreased

neutrophil function, including leukocyte chemotaxis.⁵

In part I, we discussed the epidemiology of DM and pathogenesis and prevention of DFUs. Part II

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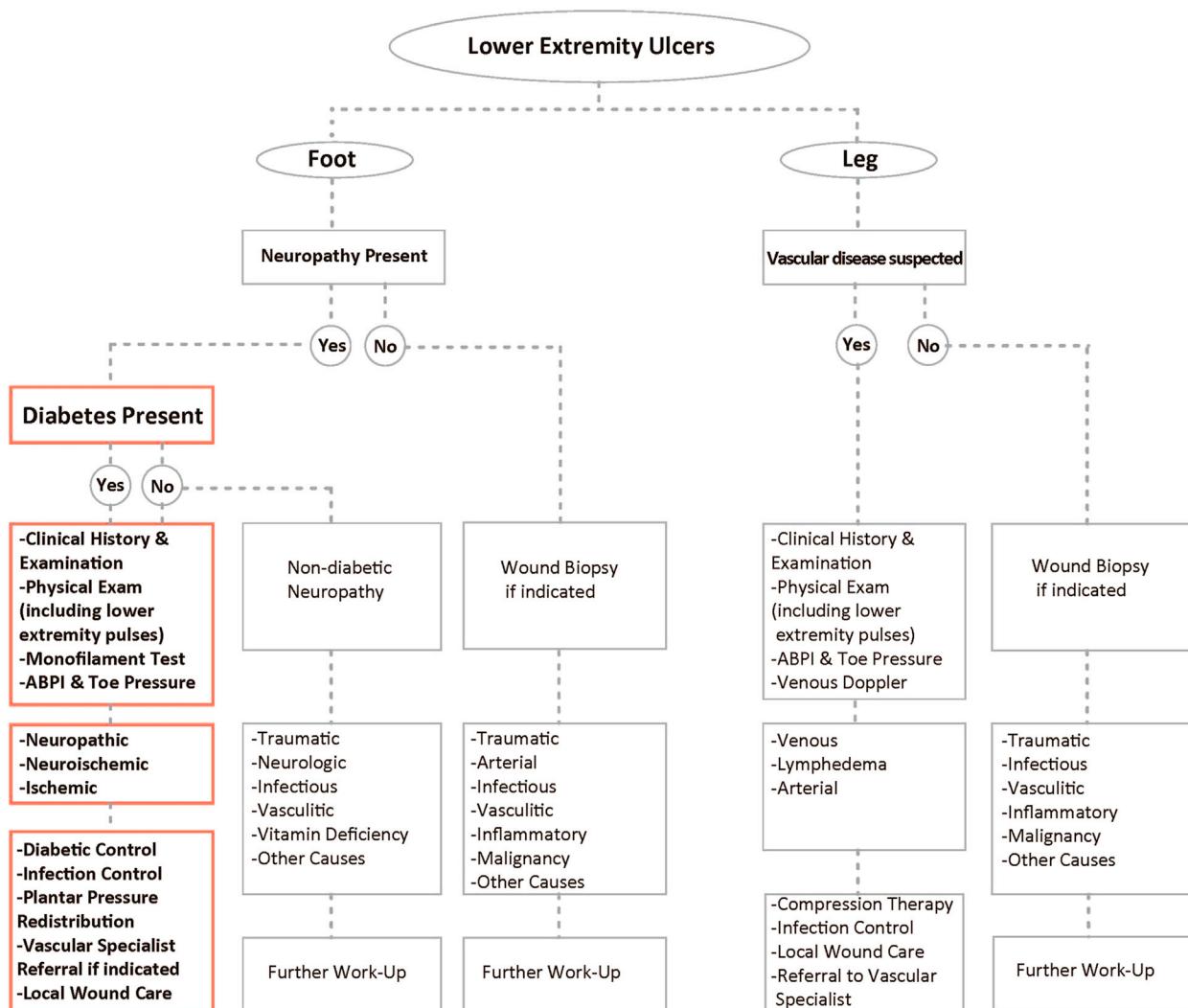


Fig 1. Suggested algorithm for the management of lower extremity ulcers.

focuses on the following key points in the management of DFUs: assessment of the diabetic foot; infection control; local wound care; wound debridement; plantar pressure redistribution; the role of surgery; wound dressings; topical antimicrobials; and advanced therapies.

The key components of local wound care include debridement, treatment of the localized infection, and the achievement of moisture balance.

ASSESSMENT OF THE DIABETIC FOOT

Key points

- The baseline evaluation should include blood pressure and laboratory testing for complete blood cell count, creatinine, and glycated hemoglobin
- The erythrocyte sedimentation rate or C-reactive protein level may be considered if a concern for osteomyelitis exists

- Early referral, vascular assessment, imaging, and intervention are crucial to prevent the complications of peripheral arterial disease in a patient with diabetes
- A falsely high ankle-brachial pressure index occurs in patients with diabetes mellitus (>1.3 is caused by glycosylation or calcification leading to noncompressible vessels)
- The toe-brachial pressure index should be measured in patients with diabetes mellitus whenever possible, and the toe pressure should be >55 mm Hg for adequate peripheral circulation to heal
- An ankle-brachial pressure index <0.4 , toe pressure <30 mm Hg, and monophasic flow by handheld Doppler ultrasound indicate severe arterial disease and represents a significant risk for delayed healing or a non-healable wound

- **A baseline radiograph of the affected foot is useful for patients presenting with a new diabetic foot ulcer**
- **Magnetic resonance imaging is the most accurate available imaging for the diagnosis or exclusion of osteomyelitis**

A comprehensive assessment including history and a physical examination is required for all patients with DFUs. Other aspects that should be reviewed include the presence of neuropathic or nociceptive pain along with a loss of protective sensation. Patient-centered concerns that should be documented include activities of daily living, the presence of depression, and alcohol consumption and smoking.

Wound assessment

The following wound-related items should be evaluated:

- Location on the foot (ie, plantar, forefoot, mid-foot, heel, dorsum, toes, or sides of foot)
- Size (ie, at least longest length with the widest width at right angles in cm or mm, ideally planimetric or computerized photography measurement)
- Depth (cm or mm) measured with a probe, and check base for exposed tendon or bone
- Appearance of the wound base (ie, granulation, fibrin, slough, or necrotic tissue [black])
- Amount (ie, none, scant, moderate, or heavy) and type of exudate (ie, serous, sanguineous, purulent, or combinations)
- Periwound skin (ie, edge or wound margin): presence of callus, maceration, or erythema
- Pain level should be evaluated: timing with dressing change or between dressing changes, severity and type of pain (ie, nociceptive [gnawing, aching, tender, or throbbing] or neuropathic [burning, stinging shooting, or stabbing] or loss of protective sensation).

This framework allows clinicians to monitor wound healing or progression. In addition, several studies have noted the role of monitored wound and periwound temperature (which is often not routinely measured) through infrared thermometry to identify surrounding tissue injury. A temperature difference of $>3^\circ$ of 4° when compared to the contralateral limb should raise a concern of infection when it is in concordance with the clinical symptoms.^{6,7} Increased temperature may also indicate deep inflammation (such as Charcot foot often in the absence of an ulcer) or unequal vascular supply, with clinical features used to differentiate these conditions. In addition, during diabetic patient

self-monitoring at risk for development of DFU, an increased local temperature may indicate a risk of skin breakdown.⁸

Although elevated temperature may be suggestive of infection, documenting additional clinical signs makes the definitive diagnosis of wound infection. The clinical diagnosis of osteomyelitis in patients with DM may be challenging. The probe to bone test by a sterile blunt stainless steel probe is helpful.⁹

Laboratory studies

Wound healing can be delayed in the presence of coexisting systemic disease or comorbidities (ie, renal or peripheral vascular disease). The baseline laboratory evaluation in a patient with DM and a foot ulcer should include a complete blood cell count, creatinine level, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level, and HbA1c level.¹⁰ Several laboratory results may be important for management. Anemia may delay healing, and leukocytosis may be associated with infection. High levels of creatinine (suggestive of renal dysfunction) may indicate a greater risk for DFU complications and alter the choice and the dose of antibiotic therapy. An ESR >40 mm per hour or a CRP >20 mm per hour is commonly associated with deep tissue infection or osteomyelitis.^{11,12} As noted above, HbA1c is a good indicator of diabetes control over 90 days. The American Diabetes Association recommends a level of HbA1c <0.07 (7%) for adults, but for the elderly and developing world and patients with brittle DM, a target of <0.09 (9%) has been suggested to avoid hypoglycemic episodes.^{13,14} Nutritional assessment, including the level of albumin, should be performed in persons with chronic wounds.¹⁵ Prealbumin has a shorter half-life than albumin and may better detect improvement in patients with protein deficiencies.¹⁶

Patients with DM, especially those with poor glycemic control, have a relative immunodeficiency. They may not present with the classic overt signs of infection.^{17,18} High levels of HbA1c have been associated with diabetic comorbidities, such as neuropathy, coronary artery disease, retinopathy, and nephropathy. Elevated HbA1c has been shown as a predictor of the development of DFUs, but additional studies are still required.⁵

Vascular assessment

A vascular assessment, when indicated, should include advanced imaging and vascular intervention. Early intervention is important to prevent complications of PAD in persons with DM. Every 1% (0.01) increase in HbA1c correlates with a 25% to 28% increase in the relative risk of PAD.^{15,19} DM increases

Table I. Arterial measurements related to vascular supply of the leg*

ABPI	Toe pressure (mm Hg)	TBPI	Ankle Doppler wave form	Diagnosis
>0.8	>80	>0.6	Normal/triphasic	No relevant arterial disease
>0.5	>50	>0.4	Biphasic	Some arterial disease: modify compression
>0.4	>30	>0.2	Biphasic/monophasic	Arterial disease predominates
<0.4	<30	<0.2	Monophasic	High risk for limb ischemia

ABPI, Ankle-brachial pressure; TBPI, toe-brachial pressure index.

*Modified from Sibbald et al.²⁷

the risk of PAD 3.5-fold in men and 8.6-fold in women.^{15,20-22}

Vascular assessment is required for all neuropathic foot ulcers. There is no universal test to assess the vascular system. Noninvasive vascular assessments include the ankle–brachial pressure index (ABPI), toe pressure and/or toe–brachial pressure index (TBPI), and transcutaneous oxygen pressure (TcPO₂) measurement. Additional studies will be indicated based on the results of these tests.^{23,24} The ABPI Doppler ultrasound measures macrovascular arterial disease and may overestimate the true pressure reading in patients with DM because of incompressible vessels often related to calcification and advanced atherosclerosis (Table I).²⁵⁻²⁷ Up to 80% of persons with DM have falsely high ABPIs of >1.2, compared to only 20% of nondiabetic individuals.²⁷ An ABPI <0.5 may not be reliable, and a complete segmental duplex Doppler ultrasound examination of the lower extremity arteries may be required to determine the location and extent of the vascular compromise. As opposed to patients without DM who have PAD, patients with DM and PAD tend to have more distal disease.²⁸ The presence of a segmental drop in arterial pressure may indicate the potential for a correctable arterial lesion. If vascular disease is suspected and intervention planned, arterial angiography is required. Computed tomography or magnetic resonance angiography (unless dilation is planned at the same time as the procedure) may be part of a comprehensive assessment.

Imaging

Baseline radiograph. A baseline radiograph of the affected foot is useful in patients presenting with a new DFU. Plain radiographs may provide information on the presence of a foreign body, soft tissue gas that may be associated with deep infection, and bony abnormalities associated with osteomyelitis, traumatic fractures, or the multiple fractures of Charcot joint. The classic change suggestive of osteomyelitis includes cortical erosion, periosteal reaction, combined lucency, and sclerosis.¹⁶ Plain film imaging has the limitation that some radiographic changes are delayed and may take

up to a month after the clinical presentation. If osteomyelitis remains a concern, plain serial radiographs may help to monitor and exclude osteomyelitis. The other limitation of radiography is the potential for confusion between the subtle changes of osteomyelitis with early Charcot foot or neuroosteoarthropathy.

Magnetic resonance imaging. A magnetic resonance imaging (MRI) scan is the most accurate available imaging for the diagnosis or exclusion of osteomyelitis.²⁹ A sensitivity of 90% and specificity of 79% has been reported in a recent metaanalysis by Dinh et al.⁹ If MRI is not available, 3-phase bone scans are an alternative for the diagnosis of osteomyelitis.³⁰ MRI is more cost-effective and offers better sensitivity and specificity compared to 3-phase bone scan.³¹ If imaging is inconclusive, a diagnostic bone biopsy specimen should be obtained for histologic assessment, and bacterial culture is the criterion standard for diagnosing osteomyelitis. The bacterial culture may also provide an opportunity to identify the causative bacterial agent and any antibiotic sensitivities.

Musculoskeletal assessment. DM-related neuropathy can cause changes to the foot that compromise normal ambulation through several different pathways. Numerous pathogenic pathways lead to muscle atrophy and compensatory biomechanical alterations in the diabetic foot. These include claw toes, hammertoes, bunions, hallux rigidus, and Charcot changes. All foot deformities and biomechanical impairments need evaluation and treatment to avoid additional damage of the bony structure to prevent foot ulcers and subsequent amputations. Treatment mainly with orthotic shoes and pressure off-loading devices should prevent excess pressure (calluses), friction, and shear (hemorrhagic blisters) in order to prevent these unwanted complications (Table II).

Biomechanical impairments are central to pressure-induced DFUs that are easily identifiable by clinical examination. The foot and the ambulatory gait pattern should be examined in relation to the patient's footwear for both effective treatment and prevention.

Table II. Pathogenesis of diabetic foot ulcers

Pathogenesis	Consequences	Evaluation	Therapy
Hyperglycemia → Glycosylation of collagen ↑, collagenase resistance ↑ → Cross-linking of collagen ↑ → Stiffness of connective tissue	<i>Limited joint mobility</i> → high plantar pressure → callus → ulcer → infection <i>Limited skin elasticity</i> → diminished absorption of shear and pressure stress → skin cracks → ulcer → infection	ROM and dorsiflexion of the toes and ankles Inspection	<i>Nonoperative</i> Physiotherapy: stretching; orthotics: outsole modifications: rocker, roller, AFO; skin care, seamless socks <i>Operative</i> Tendon release
Hyperglycemia → Abnormal fatty acid metabolism / decreased nutritional delivery	<i>Atrophy of plantar fat pads</i> → diminished absorption of shear and pressure stress → callus → ulcer → infection and damage of deep structures (bone and joint)	Palpation	
Hyperglycemia → Myoinositol uptake ↓, glycation of neural proteins ↑, polyol activity ↑, and abnormal fatty acid metabolism → Nerve ischemia/nerve function ↓ Angiopathy → Abnormal vasa nervorum → nerve ischemia	Motor neuropathy → atrophy of intrinsic (flexor) foot muscles → diabetes-dependent foot deformities (claw and hammertoe deformity/ prominence of metatarsal heads) and dislocation of plantar fat pads → improper weight bearing/diminished absorption of shear and pressure stress → callus → ulcer → infection and damage of deep structures (bone and joints) Sensory neuropathy → <u>Loss of protective sensation</u> → improper weight bearing → high plantar pressure → callus → neuropathic ulcer → infection <u>Limited locomotory coordination</u> → micro and macro fractures/ruptures of bones, ligaments, and tendons Charcot foot → deformity or instability → improper weight bearing → high pressure plantar and/or in inappropriate footwear → callus → ulcer → infection	Inspection	<i>Nonoperative</i> Diabetes-adapted insoles, outsole modifications: rocker, roller, and widening; custom made orthopedic shoes <i>Operative</i> Tenotomy, tendon transfer, resection arthroplasty, and osteotomy
		Lack of sensation with 128-Hz tuning fork or Semmes Weinstein monofilament (10 g or 5.07) Inspection, palpation: red, warm, and swollen foot without ulcer, with (stage 1-3) or without (stage 1) deformity; radiograph and magnetic resonance imaging scans	<i>Nonoperative</i> Seamless socks, TCC, diabetes-adapted insoles; outsole modifications: rocker, roller, and widening; custom made orthopedic shoes; AFO <i>Operative</i> Ostectomy (bumpectomy), realignment corrective arthrodesis, tendon release, resection arthroplasty, and amputation

	Autonomic neuropathy → decreased sympathetic innervation (autosympathectomy) Decreased perspiration (hypohidrosis, anhidrosis) → dry and atrophic skin → diminished absorption of shear and pressure stress → ulcer → infection AV shunting ↑ → increased bone absorption → Charcot foot → deformity and or instability → improper weight bearing → high pressure plantar or inappropriate footwear → callus → ulcer → infection	Inspection, palpation: red, warm, and swollen foot without ulcer, with (stage 1-3) or without (stage 1) deformity; radiography and magnetic resonance imaging scan	
<i>Previous or diabetes-independent foot deformities</i> Hallux valgus, bunion, claw/hammertoes, pes equinus, pes cavus, club foot, and so on; sensory neuropathy	Improper weight bearing → high pressure plantar or by inappropriate footwear → callus → ulcer → infection	Inspection	Nonoperative Diabetes-adapted insoles, outsole modifications: rocker, roller, and widening; custom made orthopedic shoes; AFO Operative Tenotomy, tendon transfer/release, osteotomy, exostectomy, resection arthroplasty, realignment arthrodesis, and amputation
Inappropriate footwear and sensory neuropathy	High dorsal and plantar pressure inside the shoe → pressure ulcer → infection	Inspection	Appropriate footwear

AFO, Ankle foot orthosis; ROM, range of motion; TCC, total contact cast.

INFECTION CONTROL

Key points

- More than half of individuals with diabetic foot ulcers develop skin and soft tissue infection
- Aerobic “Gram-positive” cocci, especially *Staphylococcus aureus*, are the most common cause of initial diabetic foot infection; however, individuals with chronic foot ulcers have multibacterial organisms, including “Gram-positives,” “Gram-negatives,” and anaerobes (“microbial shift” over time)
- Osteomyelitis should be suspected if an ulcer probes to bone or exposed bone is present. Multiple-phase magnetic resonance imaging is the best noninvasive test for the diagnosis for osteomyelitis. A bone biopsy specimen with culture is the definite test for diagnosing osteomyelitis. Occasionally, treatment may still be prudent if there is a high clinical index of suspicion in the presence of an inconclusive (“negative”) magnetic resonance imaging scan
- For mild to moderate infections, initial therapy is aimed at aerobic Gram-positive cocci (until microbiology results are known). Empirical broad-spectrum therapy, often tailored to local antibiotic biograms (in vitro sensitivity), is indicated for severe infections
- The duration of antibiotic therapy for mild infection should be at least 2 weeks. For moderate to severe infection, 2 to 4 weeks of antibiotic therapy is suggested, but clinical signs should determine the length of therapy

Diabetic foot infections are one of the most frequent and severe complications seen in individuals with DM. More than 50% of DFUs develop infection. There is a 10-fold increased chance of being hospitalized with a bone or soft tissue infection in a patient with DM compared to an individual without DM.³²

All wounds are contaminated and often colonized; the relative importance of bacteria may vary. Wound contamination is the presence of nonreplicating bacteria on wound surface, and wound colonization is replication of bacteria without tissue injury or immune response. Critical colonization involves the replication of bacteria in the superficial wound base with tissue damage. As host resistance weakens, the bacteria invade the wound margins and base where a critical threshold of 10^5 bacteria per gram of tissue is often associated with tissue damage by the inflammatory cytokines.³³ This wound perimeter infection often involves a

continuum between the ulcer base and the ulcer edges, where the classical signs of infection may be absent.³⁴ Bacteria react to hostile environments by producing biofilms that provide bacterial protection against the host immune response. The differentiation between a wound in bacterial balance, critical colonization, and deep and surrounding tissue infection can be challenging because contamination and colonization would not require antibiotic therapy.

The clinical signs of infection can be dampened because of diminished leukocyte function, PAD, and neuropathy.¹⁵ About 50% of patients with DM and deep foot infection lack a systemic inflammatory response indicators of infection (ie, diminished or lack of elevation of ESR or CRP, with a normal white blood cell count and body temperature), leading to a delayed diagnosis.¹¹ Uncontrolled DM can result in immunopathy with a blunted cellular response to foot infections. Impairment of macrophage function as the key player of tissue repair contributes to delayed healing and increased susceptibility to infection.³⁵

Infection is often a precursor to amputation. Peters et al³⁶ reported that with previous amputation, PAD, and neuropathy were significant risk factors for diabetic foot infection. Patients with an amputation are more likely to undergo another amputation on the remainder of their foot, lower leg, or on the contralateral leg.^{37,38} In addition, a partial foot amputation can lead to increased plantar foot pressure on the decreased remaining plantar surface.³⁹ Prevention or early treatment of infection might therefore prevent subsequent additional amputations.

The diabetic foot infection requires a multiprofessional approach with attention to local and systemic factors.^{29,40} Aerobic Gram-positive cocci, especially *Staphylococcus aureus*, are the most common cause of diabetic foot infection. Individuals with chronic foot ulcers and previous antibiotic therapy often have infections with both Gram-positive and -negative organisms. Gangrenous and severely ischemic ulcers are commonly coinfected with anaerobic pathogens.²⁹ The diagnosis of infection is clinical by identifying associated symptoms and signs such as redness, edema, increased temperature, and pain (Fig 2).

Laboratory examinations have limited use in the diagnosis of infection except in cases of osteomyelitis. However, a semiquantitative bacterial swab test—or preferably a tissue biopsy specimen—for the identification of bacterial organisms on culture and organism sensitivity can be taken before starting antibiotic therapy.⁴⁰



Fig 2. Diabetic foot infection. Neuroischemic foot with trauma at the plantar surface of the first metatarsal head leading to the spread of the plantar infection to the dorsal surface of the foot.

If bacterial swabs are to be performed, they should be taken after the wound is cleaned and debrided. The bacterial swab may detect resistant organisms and help redirect antibiotic therapy if patients do not respond to empiric therapy. The swab should be placed on “healthy appearing” tissue and pressed to just extract fluid and then rotated 360° (ie, the semiquantitative Levine technique).⁴¹ This technique has been shown to correlate best with quantitative tissue biopsy results.⁴¹ Most laboratories process specimens in a semiquantitative fashion and provide results such as scant, mild, moderate, or heavy growth. The presence of heavy growth indicates more than 10^5 colony-forming units per gram of tissue.⁴²⁻⁴⁴ Lavery et al⁴⁵ found that clinical findings may be predictive of soft tissue infection, including probing the wound to bone, long wound duration (>30 days), recurrent wounds, and traumatic wounds with associated ischemia. The diagnosis of infection is not based on culture results and therefore only leads to systemic antibiotic treatment when associated clinical signs are present (eg, enlarging wound size, satellite areas of breakdown, surrounding cellulitis, and probing to bone).

Following the clinical diagnosis of infection, empirical treatment may be followed by culture and sensitivity results that lead to a more specific choice of antibiotic therapy. Elevation in ESR over 40 mm per hour and CRP levels double the normal range, in the absence of other inflammatory conditions, may serve as diagnostic indicators suggesting osteomyelitis.⁴⁶ However, as noted above, in most patients imaging is used to diagnose osteomyelitis.⁴⁷

Osteomyelitis is a potential complication in any chronic, deep ulcer that overlies a bony prominence. Ulcers that probe to bone or exposed bone are likely to be associated with osteomyelitis.^{9,48} Grayson et al⁴⁸ studied 75 hospitalized patients with DFUs and reported that probing to bone or exposed bone

is likely to be consistent with osteomyelitis (positive predictive value, 89%).⁴⁹ A second study by Lavery et al⁵⁰ of 247 outpatients with DFUs found that those wounds that did not probe to bone were unlikely to have osteomyelitis present (negative predictive value, 0.98). MRI is useful, but if osteomyelitis is suspected clinically, systemic antibiotic therapy to treat soft tissue infection should be initiated (even in the absence of an MRI scan) for 2 to 4 weeks. Occasionally, osteomyelitis is diagnosed by bone culture taken after a “negative” MRI scan.

It has been suggested that delayed healing may be caused by the presence of a biofilm. Biofilms are densely packed aggregations of microbes that stick to each other and to a surface and are encased in a self-synthesized extracellular polymeric substance.^{51,52}

Biofilms are difficult to treat because the glycocalyx structure of the biofilm protects the bacteria and renders antimicrobial therapy less effective.⁵³ Biofilms are likely most common on the wound surface and favor surfaces of different viscosity that may be created by undebribled slough on the wound surface. The presumed removal of the surface containing biofilm through debridement either with or without biologic agents improved wound healing rates.⁵⁴

While still under investigation, the best antimicrobial agents to penetrate biofilms have a low molecular weight and include various iodine preparations.⁵⁵

For mild to moderate infection, therapy should be aimed at aerobic Gram-positive cocci. Broad-spectrum empirical therapy is indicated for severe infections (“microbial shift”). The antibiotic needs to be continued until the clinical signs resolve and/or abnormal or pathologic laboratory tests return to normal (the ESR is often slower than the CRP to return to normal). Antibiotic therapy is often not necessarily in the later stages of healing. The severity of infection determines the initial route of therapy. In some cases, oral therapy can be given, but intravenous (parenteral) therapy is indicated for all severe and some moderate infections that can be switched to oral agents as the patient improves.⁴⁰

Soft tissue infections based on Infectious Disease Society of America guidelines are classified into 3 main categories: mild (superficial tissue and limited in size and depth), moderate (deeper or more extensive), and severe (associated with systemic signs or metabolic abnormalities).³⁰ For mild infections, 2 weeks of oral antibiotics usually suffice, although some patients require an additional 1 to 2 weeks. Moderate to severe infections require at least 2 to 4 weeks of antibiotic therapy, and if bone is

involved (ie, osteomyelitis is present), usually 6 to 12 weeks minimum treatment is required. If the infected bone is removed, a shorter treatment period is often sufficient, but treatment time should be determined by the resolution of clinical signs.⁴⁰ In individuals with signs associated with deep and surrounding wound infection, systemic antimicrobial therapies (at least initially) are indicated. Most antibiotic recommendations include coverage for Gram-positive, Gram-negative, and anaerobic organisms. The recent emergence of antibiotic resistant bacteria presents a major challenge for the successful treatment of diabetic foot infections.^{30,38,56}

Local wound care

Optimal local wound care includes proper cleansing (using normal saline or sterile water), debridement of calluses and wound base especially if associated with devitalized tissue, control of localized infection, and abnormal prolonged inflammation and moisture balance. This needs to be accompanied by systemic treatment for deep and surrounding infection for successful treatment. Wound cleaning is the process of removal of loose inflammatory materials and debris from the wound surface.⁵⁷ The selection of the appropriate wound cleanser is important to minimize chemical and mechanical damage. The standard of the care for wound cleansing is to use agents with low cytotoxicity, including water, isotonic normal saline, and short contact acetic acid. Soaps and detergents have been commonly used for wound hygiene. There is evidence that these surface-active agents raise the surface pH and interfere with healing through altering the cell viability and tissue function.⁵⁷ Isotonic normal saline (0.9% NaCl) is a good cleanser for the majority of wounds, and a Cochrane review found that water is a suitable alternative.⁵⁸ The evidence regarding commercial wound cleanser safety is very limited. However, the Cochrane review concluded that there is no evidence that tap water as a wound cleanser increases the risk of infection.⁵⁸

WOUND DEBRIDEMENT

Key points

- Active (surgical) debridement (ulcer edge and base) is an adjunct to plantar pressure redistribution as the standard of care in the treatment of diabetic foot ulcers
- Additional maintenance removal of callus at every visit is of importance to avoid additional pressure and shear forces
- The main categories of debridement are surgical, autolytic, enzymatic, mechanical, and biologic

- The most selective and fastest type of debridement is sharp surgical debridement

The development of a callus on the plantar aspect of the foot indicates increased uncorrected local pressure with the loss of protective sensation (Fig 3). Removal of a callus also significantly reduces peak plantar pressure.⁵⁹ The most effective way of removing hyperkeratotic callus at the wound edge is sharp surgical debridement (Fig 4). Classically, callus removal is performed in combination with the removal of all necrotic devitalized tissue in the wound bed as the standard debridement. Different instruments may be used for debridement (Fig 5). More recently, the concept of debridement has been extended to also include removal of the following: (1) bacteria, including biofilm in the surface compartment of the wound bed; (2) unresponsive cells, such as fibroblasts in the wound bed, with a number of studies suggesting the benefit of serial debridement^{60,61}; and (3) abnormal keratinocytes at the wound edge.

Histologic assessment of the chronic nonadvancing wound edge reveals a hyperkeratotic epidermis and a necrotic dermis because of repetitive pressure injury.⁶² The activation of keratinocytes at the nonhealed edge is abnormal, and this lack of keratinocyte migration impairs healing. Activated keratinocytes in the nonhealing edge of an ulcer reveal nuclear localization of beta-catenin that consequently leads to the downstream activation of c-Myc and the inhibition of keratinocyte migration.⁶² The microanalysis of genes in the chronic wound edge reveals a reduction of epidermal growth factor receptors that also causes a decreased keratinocyte response.⁶²

A randomized controlled trial (RCT) conducted specifically to determine the effect of debridement has not been performed. Steed et al⁶³ did conduct a secondary analysis of the role of debridement in a RCT of diabetic neuropathic foot ulcers that compared the local application of placebo and recombinant human platelet-derived growth factor (rhPDGF) until complete healing or week 20. All patients had aggressive sharp wound debridement and evidence-based clinical best practices before randomization and repeat debridement of callus and necrotic tissue as needed. In their study, statistically significant enhanced complete wound healing was found with rhPDGF (48% vs. 25% with placebo [$P = .01$]). Secondary analysis also revealed that in centers where the ulcers were adequately debrided more frequently, their outcomes were superior. For example, in 1 center that performed debridement at 81% of the visits, there was 83% complete healing with rhPDGF, while in a center that debrided 15% of the

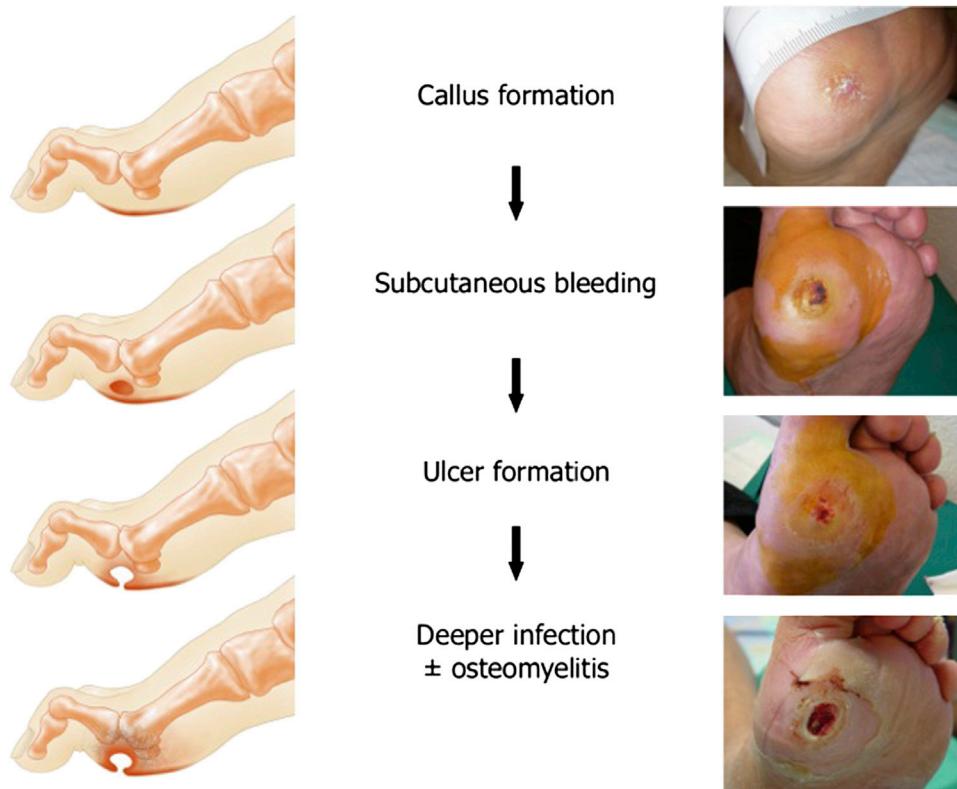


Fig 3. Stepwise process from callus formation to ulceration and infection.

visits, there was 20% complete healing (again with best practices and rhPDGF).

Falanga et al,⁶⁴ Steed et al,⁵⁵ and Cardinal et al^{60,63} have all proposed the concept of maintenance debridement after initial excisional debridement. This method of debridement depends on patient characteristics, preference, and the practitioner's level of expertise. If surgical debridement is performed, the goal is often to reach bleeding tissue, implying that adequate arterial flow is needed (Fig 6, A-C). Warriner et al⁶⁵ found, in a real-world population, that more frequent visits and sequential debridement had healing benefits, with implications of lower costs and higher quality of life for patients.

PLANTAR PRESSURE REDISTRIBUTION

- **The total contact cast is the criterion standard off-loading device, but it is contraindicated for heel ulcers, deep infection, or peripheral arterial disease**
- **The removable cast walker is reusable, easy to apply, and less expensive, but the adherence to treatment is often lower**
- **Therapeutic shoes with accommodative insoles that redistribute high-pressure areas are often used for heel ulcers and required to prevent recurrences post-ulcer healing**

- **Surgery for restoration of limited joint mobility (eg, lengthening of the Achilles tendon) or correction of deformities (eg, exostosectomy, osteotomy, resection arthroplasty, or corrective arthrodesis) may be considered in appropriate patients and may be more effective than orthopedic devices to provide plantar pressure redistribution or offloading**

Surgery for the restoration of limited joint mobility (eg, lengthening of the Achilles tendon) or correction of deformities (eg, exostosectomy, osteotomy, resection arthroplasty, or corrective arthrodesis) may be considered in appropriate patients and may be more effective than orthopedic devices to provide plantar pressure redistribution or off-loading.^{66,67} Several studies have concluded that plantar pressure redistribution is the most important component in the management of neuropathic ulcers. Therefore, inadequate plantar pressure redistribution is associated with delayed healing.⁶⁸ Wu and Armstrong⁶⁹ and Lavery et al⁷⁰ documented that the rate of healing with a total contact cast (TCC) was superior to other off-loading devices, with healing rates reported as high as 100% for appropriately selected diabetic neuropathic foot ulcers and with a mean healing time of 28 to 38 days.



Fig 4. Sharp surgical debridement. Removal of periwound ketatotic callus material using a blade. Note that the plantar hallux wound has been debrided back to the fullest extent of its undermining.



Fig 5. Debridement tools (from *left*: loop curettage, blade, Metzenbaum scissors, and Adson tissue forceps).

TCC is the application of fiberglass or other casting material to the entire lower limb, from the base of the toes to the knee, with minimal padding to mold a cast closely to the contours of the foot and the lower leg. Part of the benefit of TCC is likely because of forced adherence to the nonremovable device. In addition, by limiting activities of daily living and mobility, fewer steps are taken by the patient. However, limitations in daily living may interfere with the ability to drive and can be problematic for accompanying persons when rolling over in bed at night. The rocker bottom plantar surface and the potential for limb discrepancy with these devices may lead to discomfort in the knees and hips, especially in persons with preexisting arthritis. TCCs and removable cast walkers are effective in transferring pressure from the forefoot to the lower leg and heel, but they should not be used for heel ulcers. A RCT comparing the effectiveness of TCC, removable case walkers, and half shoes reported higher healing rates in a shorter amount of time with TCC in comparison to 2 other commonly used off-loading



Fig 6. A to C. A callus indicates continued excess pressure, and removal will facilitate healing.

modalities.⁷⁰ Studies have reported that patients wear their removable offloading devices only 25% to 28% of their total ambulatory time.⁷¹ Neuropathic plantar ulcerations require aggressive and effective off-loading in order to achieve wound healing. This requires a comprehensive interprofessional approach for the correction of intrinsic (eg, foot deformities) and extrinsic factors (eg, trauma or repetitive injury caused by footwear).

Various off-loading devices can achieve pressure redistribution, but adherence to using an off-loading device is critical. Patient education regarding alteration of gait pattern (eg, swing gait or cane on the opposite hand) may support pressure reduction.⁷² Plantar pressure measurement within the shoes or foot scanners known as pedobarography (transducers that detect up to 950 pressure points between the device and the plantar surface either stationary or with active gait) may detect the area(s) of high pressure. The choice of plantar pressure redistribution strategies is multifactorial, including the patient's age, balance, strength, activities of daily living, and home and work environment.⁷³

The selection of an appropriate off-loading device is individualized, and activity level or ability to walk with a rocker bottom heel (poor balance and loss of proprioception with neuropathy that may result in falls) is a key factor in the individualized decision of plantar pressure redistribution devices.

Therapeutic shoes with accommodative (but relatively stiff) insoles to redistribute high-pressure areas are required for some heel ulcers, when other devices cannot be worn. These devices are also important for maintenance therapy after healing to prevent recurrences. These therapeutic shoe options represent a relatively less expensive treatment option for long-term use. Therapeutic shoes and viscoelastic plantar inserts function as artificial shock absorbers to decrease the risk of foot ulceration by providing an extrinsic accommodative and protective mechanism. The rate of reulceration in the group wearing therapeutic shoes was still as high as 28% to 50%.⁷⁴ There is a need for proper footwear during nonworking hours (eg, adequate substitution for or especially manufactured therapeutic home footwear, supportive slippers, or sandals with side support and no strap between the first and second toe⁷⁴; Table III^{45,68,70,75-81}). Uncontrolled edema of the lower leg and foot has been shown by Armstrong et al⁸² to delay the healing of foot ulcers. If the edema is caused by venous insufficiency and arterial circulation is adequate, compression bandages should be used. Compression should be modified for patients with mild arterial disease and not be used for more significant arterial disease. Foot edema can also result from congestive heart failure or low albumin (eg, liver damage, kidney disease, and poor nutrition) where additional alternative corrective action is required.

There are many factors that may influence health behaviors and adherence. Because of neuropathy, many people with diabetes lack protective foot sensation. In addition, what often occurs is that the patient will wear their device while they are outside

of the home but remove it when they get home. This negates much of the benefit that was obtained from having worn the device outside of the home. Not only will the patient remove the device, but also many patients report that they will walk in stockings alone or barefoot around the house. It is important to educate both the patient and their circle of care about the negative consequences of this behavior. The removal of devices around the home is one of the primary reasons that removable devices often have much longer healing times and lower healing rates than other options that are not removable. The concept of a nonremovable device creating "forced compliance" is a way to increase patient adherence to treatment. Patient education programs need to emphasize the patient's responsibility for their own health and well-being. In many diabetes education circles, this is referred to as patient empowerment. However, patient education should not only focus on wearing appropriate footwear but also on other aspects of putting them at risk to foot ulceration. These modifiable behaviors that inhibit healing include foreign bodies within the shoes that can be detected by checking the shoes, eliminating foot baths, measuring water temperature for baths with a thermometer, avoiding heating cushions in winter, and exercising caution with personal foot care, especially nail cutting. Regular visits to a foot care specialist are optimal, especially in high-risk individuals that include those with impaired vision or neuropathy.

ROLE OF SURGERY IN THE MANAGEMENT OF DIABETIC FEET

Diabetic foot surgery has a role in the prevention and management of DFUs. Although the surgical intervention in these patients is not without risk, the selective correction of chronic deformities and persistent foot ulcers can improve outcomes.^{82,83} Surgery has an important role in the reconstruction of soft tissue defects in these patients.⁸⁴ Careful consideration of the indications for diabetic foot surgery should always include the presence of sufficient arterial perfusion for healing.^{66,67}

While the aim of management of the diabetic foot focuses on limb salvage, in select cases amputation may offer a better functional outcome, although this often is not clearly defined. This decision is very individualized and multifactorial to match the patient's lifestyle and their medical, physical, and psychological comorbidities.⁸⁵ In general, amputation should be the last resort after all other salvage techniques have been explored and the patient must

Table III. Common plantar pressure redistribution devices

Off-loading device	Advantages	Disadvantages	Cost (USD)*
Total contact cast	Criterion standard; reduces pressure under ulcer site between 84-92%; forced patient adherence to device	Requires trained professional to apply; can result in secondary ulceration with improper application; contraindicated for infected or ischemic wounds; use with caution for heel ulcers	\$\$\$\$ and additional \$\$ for application (average cost of 12 wks)
Removable cast walker	Can be used for infected wounds; can be made irremovable to become instant total contact cast	Removable; patient needs time to learn how to use it; contraindicated for heel ulcers and poor balance	\$\$, dependent on device model
Half shoe (forefoot)	Transfers pressure to mid- and rearfoot by eliminating propulsion; low cost	Very unstable; contraindicated in patients with gait instability; high risk of falls	\$/device
Padding/felted foam	Low cost	Off-loading property limited; can cause high pressure "edge effect"	\$/application

Custom made orthotics	Distributes pressure under foot evenly; may be used with over the counter footwear [†]	Requires trained professional to assess and mold/modify; relatively higher cost	\$\$\$
Custom braces, ankle and foot orthoses	Immobilize the foot and ankle to manage wounds	Inhibits motion of the foot and ankle; can require a deeper shoe	\$\$\$\$

*\$, <\$100; \$\$, \$100-500; \$\$\$, \$500-1000; \$\$\$\$, \$1000-2000; \$\$\$\$\$, >\$2000.

[†]Off the shelf shoes: primarily used for prevention, but required to be used in conjunction with padding or custom orthotics.

Table IV. Primary and moisture balance dressings for diabetic foot ulcers^{48,56}

Class	Description	ABS	DEB	INF	Advantage/disadvantage
Films/membrane	Semipermeable adhesive sheets	—	X	—	<i>Advantage(s):</i> Translucent, permeable to water vapor <i>Disadvantage(s):</i> Adherent; nonabsorbent, if fluid collects under film it must be drained or the film replaced
Nonadherent	Sheets of low adherence to tissue	—	—	—	<i>Advantage(s):</i> Thin, flexible <i>Disadvantage(s):</i> Nonabsorbent, but bacteria can penetrate laterally
Hydrogels (amorphous)	Polymers with high water content	X	XXX	—/X	<i>Advantage(s):</i> Provides moisture, nonpainful <i>Disadvantage(s):</i> Needs secondary dressing, caution in infected wounds
Acrylics	Clear film	X	XX	—/X	<i>Advantage(s):</i> Opaque, permeable to water vapor <i>Disadvantage(s):</i> Low absorbency, sometimes difficult to remove
Hydrocolloids	Hydrophilic carboxy part and methycellulose is hydrophobic bound to polyurethane film; also adhesive with or without gelatin/pectin	X	XXX	—	<i>Advantage(s):</i> Autolytic debridement; self-adherence; long wear time; impermeable to fluids <i>Disadvantage(s):</i> Low absorptive capacity; potential trauma with removal; pentalyn H in some hydrocolloid adhesives may cause allergies, and this cross-reacts with colophony
Calcium alginates	Sheets—wick laterally, ropes wick upward; from seaweed/kelp	XX	XX	X	<i>Advantage(s):</i> Hemostatic; autolytic debridement; fluid bound to outer fibers <i>Disadvantage(s):</i> Needs secondary dressing; bioresorbable, but retained fibers can be hydrated to facilitate removal
Hydrofibers	Sheets or ribbons of carboxymethylcellulose	XX	—	X/—	<i>Advantage(s):</i> Highly absorptive; fluid lock; nontraumatic on removal <i>Disadvantage(s):</i> Needs secondary dressing; may reach saturation
Foam adhesive	Polyurethane foam fluid exchange with partial fluid retention	XXX	—	—	<i>Advantage(s):</i> Absorbent; different pore sizes will give partial retention; can serve as delivery vehicle for silver, polyhexamethylene biguanide hydrochloride, and ibuprofen <i>Disadvantage(s):</i> Bulky; may macerate surrounding skin
Composite or absorptive island dressings	Multilayered combination to increase absorbency—fluid lock and autolysis	XXX	X/-	—	<i>Advantage(s):</i> Highly absorptive for high levels of exudate; relatively cheap, diaper-like technology <i>Disadvantage(s):</i> Bulky
Charcoal	Odor absorbing charcoal	X/-	—	—	<i>Advantage(s):</i> Odor control that is less effective when the charcoal is wet

ABS, Absorbency; DEB, debridement; INF, infection.

Table V. Antimicrobial dressings for diabetic foot ulcers

Antiseptics/antimicrobials	Bacterial sensitivity	Effect	Adverse effect
<i>Iodine-based</i> Povidone iodine, 10% solution, Cadexomer iodine, and Inadine (available in Europe and Canada, but not in the United States)	<ul style="list-style-type: none"> Broad antibacterial effect (Gram-positives more than Gram-negatives) and MRSA Good penetration of biofilms 	<ul style="list-style-type: none"> Short-term treatment and reassess every 2-4 wks Cadexomer iodine releases the iodine slowly to make it less toxic + cadexomer sugar for autolytic debridement + absorbency Antibacterial effect (0.005% concentration) without tissue toxicity 	<ul style="list-style-type: none"> Can be toxic to granulation tissue Antimicrobial action may be neutralized by inorganic and organic agents Thyroid dysfunction Can develop an allergy
Chlorhexidine, polyhexamethylene biguanide hydrochloride, a derivative of chlorhexidine—foam and gauze Acetic acid, white vinegar 5%	<ul style="list-style-type: none"> Gram-positives more than Gram-negatives, yeast, mold Gram-negatives, particularly <i>Pseudomonas</i> 	<ul style="list-style-type: none"> 0.02% concentration has been used for wound irrigation Promotes wound healing⁶³ Compresses 5-10 min Dilute 1:5 (1%) or 1:10 water (0.5%) 	<ul style="list-style-type: none"> May damage cartilage/ear toxicity^{64,65}
<i>Silver compounds</i> Silver dressings, foams, calcium alginates, hydrofibers, hydrogels, sheets, and powder; silver sulfadiazine cream; silver nitrate sticks	<ul style="list-style-type: none"> Antibacterial, including <i>Escherichia coli</i>, <i>Klebsiella</i>, <i>Staphylococcus aureus</i>, and MRSA Antifungal Antiviral 	<ul style="list-style-type: none"> Must be combined with water to be in the ionized state—Ag +, ++, and +++ Silver nanoparticles enhanced contact and bactericidal activity Antiinflammatory effect may relate to the Ag 0 state 	<ul style="list-style-type: none"> High concentration and long contact May have some tissue toxicity and inhibits fibroblast growth Silver toxicity to reepithelialization process Toxicity much less with dressings than silver Sulfadiazine cream with much higher silver release Sticks plus silver sulfadiazine cream may produce proinflammatory pseudoeschar/delay healing Potential risk of botulism with food product honey⁶⁴
Honey (medical grade; often Munuka honey), calcium alginate; hydrogel; hydrocolloid	<ul style="list-style-type: none"> Antibacterial Antifungal Antiviral 	<ul style="list-style-type: none"> Antiinflammatory High osmolar concentration contributes to the antibacterial effect 	<ul style="list-style-type: none"> Irritant with high tissue toxicity Inhibit fibroblast in 1% concentration Best used as disinfectant and not for wound care Very high tissue toxicity
Sodium hypochlorite (bleach)	Broad antibacterial effect (Gram-positives more than Gram-negatives)	Antibacterial effect (0.005%) without lower tissue toxicity	
Benzalkonium chloride	Gram-positive and -negative, fungi	Compromised bactericidal activity because of neutralization with organic matter in tissue fluids	
Hydrogen peroxide	Gram-positive bacteria with 3% concentration	<ul style="list-style-type: none"> Limited mechanical debridement Biofilm reduction 	<ul style="list-style-type: none"> Bulla formation Risk of air emboli⁶⁷ if applied to deep cavities

MRSA, Methicillin-resistant *Staphylococcus aureus*.

be in agreement. Although distal arterial bypasses below the knee are more frequently undertaken, some patients do not have dilatable or bypassable lesions. Allowing dry gangrene to demarcate and having distal areas (eg, toes) eventually separate and fall off may be a preferred option in some individuals, especially if they are poor surgical candidates.

Wound dressings

Key points

- **The main categories of dressings include, films, hydrogels, acrylics, hydrocolloids, calcium alginates, hydrofibers, and foams**
- **Wounds with high levels of exudate need absorptive dressings, whereas a dry wound requires moisture balance dressings that donate moisture to the wounds**

Wound dressings not only provide a physical protective barrier to the wound, but they also help maintain an optimal wound environment (homeostasis) with moisture balance to enhance healing. Highly exuding wounds require absorptive dressings, such as foams, calcium alginates, or hydrofiber dressings. Dry wounds are balanced with dressings that donate water (hydrogels) or preserve or bind water (acrylics, hydrocolloids, and films). Films either alone or as the top layer of acrylics and hydrocolloids have a low moisture vapor transmission rate that also assists in keeping the wound adequately moist. The choice of dressing is largely determined by the type of the wound and the wound characteristics, including exudate, odor, pain, or microbiology, including localized critical colonization. The main categories of the dressings are listed in Table IV.²⁷ For DFUs, the benefit from a specific dressing choice is less important than optimal off-loading. Modern moist interactive dressings do not have high quality RCTs to show a benefit over gauze. However, they have longer wear time, greater absorbency, may be less painful, and are typically less traumatic upon removal. Moreover, in certain patients, they are cost effective because of the lower frequency of dressing changes and the savings of expensive nursing time.⁸⁶ Finally, concern when using occlusive dressings in patients with DM exists. The latter, suffering from decreased immune response, are prone to exacerbation of clinically unsuspected infection when occlusive dressings (eg, hydrocolloids) are applied. We suggest being cautious with the use of occlusive moisture retaining dressings next to the wound (ie, films, hydrocolloids, and acrylics), especially if there is any suspicion of infection.

Topical antimicrobials: The role of antiseptics and other antimicrobials

Key points

- **The best options for wound cleansers are normal saline or water**
- **The topical antimicrobial of choice will be based on the agent's antibacterial but also antiinflammatory effect and the relative lower toxicity to the host granulation tissue**

The best options for wound cleansing are normal saline or water.⁸⁷ Potable (drinkable) water is acceptable for most wounds unless there is immunosuppression or a very deep cavity.^{58,87} The role of topical antimicrobials for DFU is not well defined because studies have yet to clearly show a benefit. Topical antibiotics may cause contact allergic dermatitis and do not provide moisture balance or autolytic debridement for optimal topical treatment of chronic wounds. Therefore, topical antiseptics are preferred for critical colonization because they have an antibacterial effect with lower toxicity to the host tissue. Currently available antiseptics are listed in Table V,^{88,89} and they are best administered with sustained release formulations.

Advanced therapies

Key points

- **Advanced therapies should be considered in stalled but healable wounds with optimal care and when the wound edge is not migrating**
- **Advanced biologic therapies have a role in the management of stalled wounds, including growth factors, negative pressure wound therapy, hyperbaric oxygen, and tissue-engineered ("artificial") skin**
- **The most readily available advanced therapy is autologous skin. In many countries where other advanced therapies are not available, autologous split skin graft may be the treatment of choice and may significantly accelerate wound healing by various mechanisms**
- **Reconstructive surgery may offer a more definitive solution with adequate coverage of bony prominences or weight-bearing areas, further supporting the need for interdisciplinary management of diabetic foot ulcers**

Recent advances in basic science research and related techniques have influenced the options for the treatment of chronic wounds. Sheehan et al⁹⁰ concluded that if a DFU is not 50% smaller at week 4 despite optimal care, it is unlikely to heal by week 12. An earlier decision to use advanced therapies

Table VI. Tissue-engineered skin equivalents (acellular and cellular)⁸¹

Name and description	Trade names*	Types	Graft composition
Epidermal	Epicel and Epidex	Autograft	Keratinocyte expanded from skin biopsy
Dermal (acellular)	Bioseed	Autologous	Keratinocyte in fibrin sealant
	Alloderm/Graft Jacket	Alloderm	Cadaveric decellularized dermis
	Biobrane	Xenograft	Porcine type I collagen bonded to a silicone film membrane
	E-Z Derm	Xenograft	Porcine type I collagen bonded to a gauze liner
	Integra	Xenograft	Bovine tendon collagen and shark chondroitin
	OASIS	Xenograft	Porcine intestine collagen type I and extracellular matrix
Dermal (cellular)	Dermagraft	Allograft	Allogenic—neonatal foreskin fibroblast in polyglactin suture
Bilayered	Apligraf	Allograft	Allogenic—engineered neonatal foreskin keratinocytes and fibroblasts plus bovine collagen type I

*Trade names remain property of their respective manufacturers.

improves the likelihood that these interventions will be effective.⁹¹ Several studies have shown that advanced biologic therapies in combination with standard care improve the healing of DFUs.⁹²⁻⁹⁴

Growth factors. Growth factors are biologically active polypeptides that alter the growth, differentiation, and metabolism of target cells and induce a cascade of signal transduction pathway.^{95,96} Beclapermin (REGRANEX GEL; Healthpoint, Dallas, TX), a topical recombinant human rhPDGF, is the only growth factor approved by the US Food and Drug Administration for the treatment of diabetic foot ulcers.^{88,96} PDGF is produced by platelets, macrophages, vascular endothelium, fibroblasts, and keratinocytes. Multiple RCTs have shown the role of PDGF in the healing of DFUs.⁹⁷ In a retrospective cohort study on 2517 patients with DFUs, the role of advanced biologic therapies, including PDGF in the first month, has been emphasized.⁹¹ When indicated, early treatment with PDGF has been associated with a shorter healing time of DFUs.⁹⁸ In a metaanalysis on 922 patients with DFUs, Bepacupermin gel at a dose of 100 mcg per gram administered on a daily basis has been shown to be effective with a healing rate of 83% as an adjunctive to the standard care.⁵⁴

Negative pressure wound therapy. Negative pressure wound therapy (NPWT) is the delivery of subatmospheric pressure to the wound bed. In this system, polyurethane or polyvinyl alcohol foam or gauze is cut and placed on the wound surface. The foam or gauze then is sealed by a transparent drape to provide a close airtight system. A vacuum pump is connected to this space and provides a negative pressure environment. The suction effect causes deformation of the extracellular matrix and promotes cellular proliferation.⁹⁵ In a multicenter RCT on 162 patients with DFUs and recent amputation site surgery, NPWT had a healing rate of 56%

compared to 39% in the control group, with similar adverse events in both groups.⁹⁹ NPWT was found to be safe and effective for the postsurgical treatment of acute diabetic wounds, but it has not shown effectiveness in chronic nonhealing wounds.^{100,101}

Hyperbaric oxygen therapy. Hyperbaric oxygen therapy (HBOT) is the administration of 100% oxygen to the wound through an airtight vessel at a pressure >1 atmosphere absolute.⁹⁵ Systemic HBOT sessions in the chamber last usually 45 to 120 minutes; generally, 1 or 2 sessions daily are carried out, 4 to 5 times per week, for a total of 20 to 30 sessions at a pressure 2 to 3 times greater than ambient atmospheric pressure.^{95,101-103} In a systematic review on the role of HBOT on chronic wounds, 9 RCTs (471 patients) were identified, 8 of which enrolled patients with DFUs (455 patients) with a Wagner grade from 0 to 4.¹⁰¹ Pooled data of 3 RCTs with 140 patients showed a significant ($P = .02$) increase in the rate of ulcer healing with HBOT at 6 weeks, but this benefit was not evident at longer-term follow-up (1 year). However, there was no statistically significant difference in the major amputation rate in pooled data of 5 trials including 312 patients. To date, there is still controversy about the efficacy of HBOT in the treatment of DFUs. A recent longitudinal observational cohort study by Margolis et al¹⁰¹ on 6259 individuals with diabetes, adequate lower limb arterial perfusion, and foot ulcer found that the use of HBOT neither improved the likelihood of healing nor prevented amputation in a cohort of patients defined by Centers for Medicare and Medicaid Services eligibility criteria.¹⁰¹ The authors concluded that the usefulness of HBOT in patients with DFUs needs to be reevaluated. In contrast, Löhndal¹⁰⁴ reviewed 6 individual RCTs and concluded that data evaluating HBOT in DFU treatment are more robust than evidence in favor of

many other practices in the diabetic foot treatment armamentarium, especially in patients with ulcer duration >3 months and no need or possibility of vascular surgery. Another recent prospective RCT evaluating the effects of HBOT on healing and oxidative stress of ulcer tissue in patients with DFUs suggested that HBOT treatment for 2 weeks initiates a significant healing response in chronic DFUs, but the observed oxidative stress in local ulcer tissue may offset this long-term effect; the authors concluded that prolonged HBOT should be avoided until additional research has been conducted.¹⁰⁵ Chow et al³¹ calculated that adjunctive HBOT produced an incremental cost per quality-adjusted life year at year 1 of \$27,310 US (year 2001 value). In summary, although there is some evidence that HBOT might be effective in the treatment of DFUs, larger prospective RCTs are warranted. In any case, candidates for HBOT should be screened for determinants of outcome: patients should have transcutaneous oxygen values above 30 and below 40, and these levels should double with breathing 100% oxygen with a mask.¹⁰³

Skin and skin equivalents. Bioengineered skin equivalents have the ability to repair wounds in a multifaceted way, including moisture balance, structural support for tissue regeneration, and the provision of cytokines and growth factors in a physiologic concentration. Cells from these skin substitutes often do not persist for a prolonged time but rather supply growth factors and/or extracellular matrices to speed healing. Skin substitutes are acellular or cellular (ie, epidermal cell, dermal cell, or composites¹⁰⁶; Table VI).^{95,107}

The cell-based products have the largest number of quality RCTs. In an RCT study using a dermal skin equivalent (Dermagraft; Shire Regenerative Medicine, La Jolla, CA), the rate of complete healing at week 12 was 30% with a faster time to complete healing compared to 18% in the control group.⁹² Similarly, a bilayered living skin equivalent (Apligraf; Organogenesis, Canton, MA) has been evaluated in diabetic patients, reaching a healing rate of 56% at 12 weeks compared with 38% of control patients and demonstrating a statistically significant reduction in osteomyelitis and amputation in those treated with the engineered skin construct.^{108,109} Two additional studies also noted an improved healing rate with the use of skin equivalents.^{110,111}

PSYCHOSOCIAL IMPACT OF DIABETIC FOOT ULCERS

Key point

- Diabetic foot ulcers are a source of physical and emotional distress associated with a

subsequent decreased quality of life and activities of daily living

Persons with DM that develop foot ulcers are faced with lifestyle changes on an ongoing basis because of their DM and other disease-related comorbidities and chronic complications. Balancing their DM alone (ie, controlling and monitoring blood sugar levels through dietary changes, medication, and exercise) along with blood pressure and cholesterol control can be an important burden on many of these patients. The affected patients usually require frequent wound clinic visits and ongoing recommendations on the reduction of weight-bearing-related activities. All of these restrictions can interfere with work, potential income, social life, and mobility.¹¹²

Patients with DFUs often experience depression, anger about their condition, frustration, and fear of amputation. Their frustration can be related to the restrictions in mobility and the subsequent impact on their work, lifestyle, and self-image.¹¹³ If depression is left untreated, affected patients may experience a decreased level of useful activities of daily living. Biochemically, diabetes-associated depression can be linked to abnormal circulating cytokines.^{114,115}

Clinicians managing DFUs need to ensure that their patient accepts the self-care recommendations in order to increase treatment adherence. Affected patients require ongoing reassurance and empowerment to enable them to take charge of their health and become active participants in their care plan.

CONCLUSION

Chronic wounds, including DFUs, are among the most costly and devastating conditions that dermatologists encounter. Early detection and effective management of these ulcers can reduce the severity of complications, including preventable amputations. DFUs are classified as neuropathic, ischemic, or neuroischemic. The high-risk foot can be diagnosed with a simplified 60-second screening test. Management of the diabetic foot can be optimized with an interprofessional team approach that addresses the correctable risk factors (ie, poor vascular supply, infection management, and plantar pressure redistribution [VIP]) along with optimizing local wound care. Diabetic foot care can start with the dermatologist. The first step is the recognition of a skin integrity breakdown (eg, callus, blister, or ulcer), which considerably increases the risk of preventable amputations. Early referral after identification of the high-risk foot or

recent foot ulcer often saves not only limbs but also lives.

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Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)

Part I. Diagnosis: Clinical and histopathologic features and new molecular and biologic markers

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Mycosis fungoides (MF) and Sézary syndrome (SS) comprise approximately 53% of cutaneous lymphomas. Both MF and SS may clinically and histologically mimic benign skin conditions, posing a diagnostic challenge to the dermatologist. Precise clinicopathologic correlation is necessary to support a diagnosis, especially in the early stages of disease. In addition to the identification of histopathologic criteria, ancillary studies, including the identification of CD4⁺ T cells with aberrant immunophenotypes and T-cell receptor gene rearrangements within skin lesions and peripheral blood are used to support the diagnosis. Recent studies evaluating the pathogenesis of MF have found that the skin microenvironment, including immune cells, such as dendritic cells and reactive cytotoxic and regulatory T cells, plays a crucial supporting role in MF. The skin-homing ability of malignant T cells is the result of chemokines, cytokines, adhesion molecules, and defective apoptosis, and is believed to play a role in disease pathogenesis and progression. In addition, recent studies have also suggested that MF and SS arise from distinct memory T cell subsets and advanced/erythrodermic MF and SS may be distinguished by identification of certain molecules, including Programmed-Death-1. (J Am Acad Dermatol 2014;70:205.e1-16.)

Key words: biologic and molecular markers; clinical and diagnostic challenges; cutaneous T-cell lymphoma; genetic aberrations; histopathology; mycosis fungoides; mycosis fungoides subtypes; pathogenesis; prognostic value; Sézary syndrome; skin homing features; transformed mycosis fungoides; tumor microenvironment.

Primary cutaneous lymphomas represent a heterogeneous group of T- and B-cell lymphomas that has resulted in controversy over diagnosis and classification in the past. Mycosis fungoides (MF), which is generally indolent in behavior, and Sézary syndrome (SS), an aggressive and leukemic variant, comprise approximately 53% of all cutaneous lymphomas, and are collectively referred to as cutaneous T-cell lymphomas¹ (CTCLs; Table I).

MF and SS may present with numerous variants that mimic benign skin conditions, such as eczema, folliculitis, pigmented purpuric dermatoses, psoriasis, vitiligo, pityriasis lichenoides chronica, and pityriasis lichenoides et varioliformis acuta.^{2,3} Similarly, after a histologic examination, MF can resemble inflammatory dermatoses. As a result, MF can pose a diagnostic challenge to the dermatologist. Clinicopathologic correlation is necessary to support a diagnosis in the early stages of disease. In this review, we summarize the clinical features of MF, SS, and MF variants and provide a concise review of histopathologic criteria and ancillary studies, including new genetic and molecular markers that are essential for understanding disease pathogenesis and are currently being explored as therapeutic targets.

EPIDEMIOLOGY

Cutaneous lymphomas represent 3.9% of all non-Hodgkin lymphomas, with MF comprising the majority of cases.⁴ The incidence of CTCL has risen since

Abbreviations used:

APC:	antigen-presenting cell
CLA:	cutaneous lymphocyte antigen
CTCL:	cutaneous T-cell lymphoma
E-CTCL:	erythrodermic cutaneous T-cell lymphoma
EMF:	erythrodermic mycosis fungoides
GMF:	granulomatous mycosis fungoides
HTLV-1:	human T-lymphotropic virus type 1
IL:	interleukin
ISCL:	International Society for Cutaneous Lymphoma
LCT:	large cell transformation
MF:	mycosis fungoides
PD-1:	Programmed-Death-1
SS:	Sézary syndrome
TCR:	T-cell receptor
Treg:	regulatory T cells

1973, with an annual age-adjusted incidence of 6.4 to 9.6 cases per million people in the United States.⁵ MF typically affects older individuals with a median age at diagnosis of 55 to 60 years and a male:female ratio of 2:1.^{1,4} However, MF can also be seen in younger populations, including children.^{6,7} The majority of patients (~70%) are white, with blacks, Hispanics, and Asians making up 14%, 9%, and 7% of MF cases in the United States, respectively.⁴ Patients with MF and SS are at a significantly increased risk of developing a second lymphoma, in particular Hodgkin lymphoma and the CTCL subtype lymphomatoid papulosis, as well as nonhematologic malignancies.^{5,8}

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Table I. The new World Health Organization/European Organization for Research and Treatment of Cancer consensus classification for primary cutaneous lymphomas with relative frequency and 5-year survival*

WHO-EORTC classification	Frequency (%)	5-year survival (%)
Cutaneous T-cell and NK cell lymphoma		
Indolent		
Mycosis fungoides	44	88
Follicular mycosis fungoides	4	80
Pagetoid reticulosis	<1	100
Granulomatous slack skin	<1	100
CD30 ⁺ lymphoproliferative diseases		
Anaplastic large cell lymphoma	8	95
Lymphomatoid papulosis	12	100
Subcutaneous panniculitis-like T-cell lymphoma	1	82
CD4 ⁺ small/medium pleomorphic T-cell lymphoma	2	72
Aggressive		
Sézary syndrome	3	24
Cutaneous peripheral T-cell lymphoma, unspecified	2	16
Cutaneous aggressive CD8 ⁺ T-cell lymphoma	<1	18
Cutaneous γ/δ T-cell lymphoma	<1	—
Cutaneous NK/T-cell lymphoma, nasal type	<1	—

EORTC, European Organization for Research and Treatment of Cancer; NK, natural killer; WHO, World Health Organization.

*Adapted with permission from Willemze et al.¹

ETIOLOGY

MF is believed to result from chronic antigenic stimulation that leads to uncontrolled clonal expansion and the accumulation of T cell helper memory cells in the skin.⁹ In support of this notion, increased numbers of dendritic cells were found in early MF lesions.¹⁰ Specifically, antigen-presenting cell (APC) ligands B7 and CD40 and their respective T cell costimulatory ligands CD28 and CD40L were found to be upregulated in MF lesions.^{11,12} Neoplastic T cells can also express APC ligands, suggesting a possible self-stimulation pathway that leads to T cell expansion. Other studies have shown increased Toll-like receptor expression (Toll-like receptors 2, 4, and 9) by keratinocytes and increased expression of particular human leukocyte antigen class II alleles in MF patients.^{13,14} Toll-like receptor stimulation is seen in inflammatory skin diseases, including psoriasis and chronic allergic contact dermatitis.¹⁵ Although lymphomatoid reactions caused by contact hypersensitivity have been reported, no causal relationship between contact dermatitis or other

inflammatory skin conditions and MF/SS have been identified.^{16,17}

Infections, specifically *Staphylococcus aureus* and associated enterotoxins, may also play an etiologic role in MF. One study found a high rate of *S aureus* colonization in patients with erythrodermic MF (EMF) and SS, with clinical improvement of both erythroderma and extent of skin disease after antibiotic therapy.¹⁸ Unlike adult T-cell leukemia/lymphoma, which is associated with human T-lymphotropic virus type 1 (HTLV-1), most CTCL patients are serologically HTLV-1⁻.^{19,21} Other investigators have found serologic evidence for Epstein–Barr virus and cytomegalovirus, but there is minimal evidence supporting a viral etiology.²²

Immunosuppression and/or immunosuppressive therapy may predispose patients to develop CTCL in rare cases after organ transplantation^{23–25} and in those with HIV.^{26,27} Occupational factors, such as working in the glass, pottery, and ceramics industry have been studied; however, their role in MF remains controversial.^{28,29} Military exposures, such as herbicide exposure, have been linked to non-Hodgkin lymphoma, although not specifically to CTCL.

CLINICAL PRESENTATION

Key points

- **Classic mycosis fungoides presents with patches and plaques on non–sun exposed areas that may slowly evolve to tumors**
- **Sézary syndrome is an aggressive, leukemic cutaneous T-cell lymphoma variant, characterized by a triad of circulating neoplastic T cells and erythroderma, with/without associated lymphadenopathy**
- **Erythrodermic mycosis fungoides is differentiated from Sézary syndrome by absent/low circulating Sézary cell count and is regarded as a progression of mycosis fungoides, whereas Sézary syndrome typically arises de novo**

Classic mycosis fungoides

Classic MF is a disease that progresses slowly over years and sometimes decades, presenting with well defined, often pruritic erythematous patches distributed in non–sun exposed “bathing suit” areas, including the breasts, buttocks, lower trunk, and groin (Fig 1). These patches may evolve to infiltrative plaques and tumors, and all 3 lesion types can be seen concomitantly.¹ Hypopigmented lesions are a rare presentation of MF, most often seen in children, adolescents, and dark-skinned individuals.³⁰ Approximately 30% of patients present with skin tumors or erythroderma at disease onset.³¹



Fig 1. Mycosis fungoides patients presenting with disseminated patches (**A**), plaques (**B** and **C**), and tumors (**D** and **E**). All 3 lesion types can be seen concomitantly (**E**).

Table II. Proposed classification for erythrodermic cutaneous T-cell lymphoma and relative hematologic criteria devised by the International Society for Cutaneous Lymphoma in their consensus conference on erythrodermic cutaneous T-cell lymphoma*

Erythrodermic CTCL	Preexisting MF	Blood findings	Tumor-node-metastasis-blood staging
Sézary syndrome	Rarely	Leukemic	T4, N0-3, M0-1, B2 [†]
Erythrodermic MF	Always	Absent or minimal	T4, N0-3, M0-1, B0-1 [†]
Erythrodermic CTCL not other specified	Absent	Absent or minimal	T4, N0-3, M0-1, B0-1 [†]

CTCL, Cutaneous T-cell lymphoma; MF, mycosis fungoïdes.

*Adapted with permission from Vonderheide et al.³²

[†]B0, <5% circulating Sézary cells; B1, Sézary cell count of <1000 cells/m³ or <20% atypical T cells on peripheral smear; B2, Sézary cell count of >1000 cells/m³ or >20% atypical T cells on peripheral smear.

Sézary syndrome and erythrodermic mycosis fungoïdes

SS, the aggressive and leukemic CTCL variant, is characterized by circulating atypical T cells (Sézary cells), diffuse erythema (erythroderma), and severely disabling pruritus with or without lymphadenopathy.¹ SS typically arises de novo in a short time period, although some patients may have a prodrome of pruritus and nonspecific dermatitis. It is considered separate from MF, but in rare cases, SS may follow classic MF. The International Society for Cutaneous Lymphoma (ISCL) recommends calling these cases “SS preceded by MF” to distinguish them from classic SS.³²

Erythrodermic MF (EMF) similarly presents with erythroderma and, together with SS, encompasses

erythrodermic CTCL (E-CTCL; **Table II**). EMF is generally considered to be a progression of MF and is distinguished from SS by absent or minimal blood involvement. A low tumor burden of circulating Sézary cells can be seen in EMF without meeting the criteria of SS.³³

The skin appearance in E-CTCL may vary from mild erythema to generalized exfoliative erythroderma with keratoderma and fissures on the palms and soles (**Fig 2**). These cutaneous findings are associated with electrolyte imbalances, hypothermia, hair loss, and eyelid changes/ectropion. Diagnosis may be missed in the elderly, whose symptoms of dry skin and pruritus are attributed to advanced age. Cutaneous drug reactions, infections, generalized seborrheic

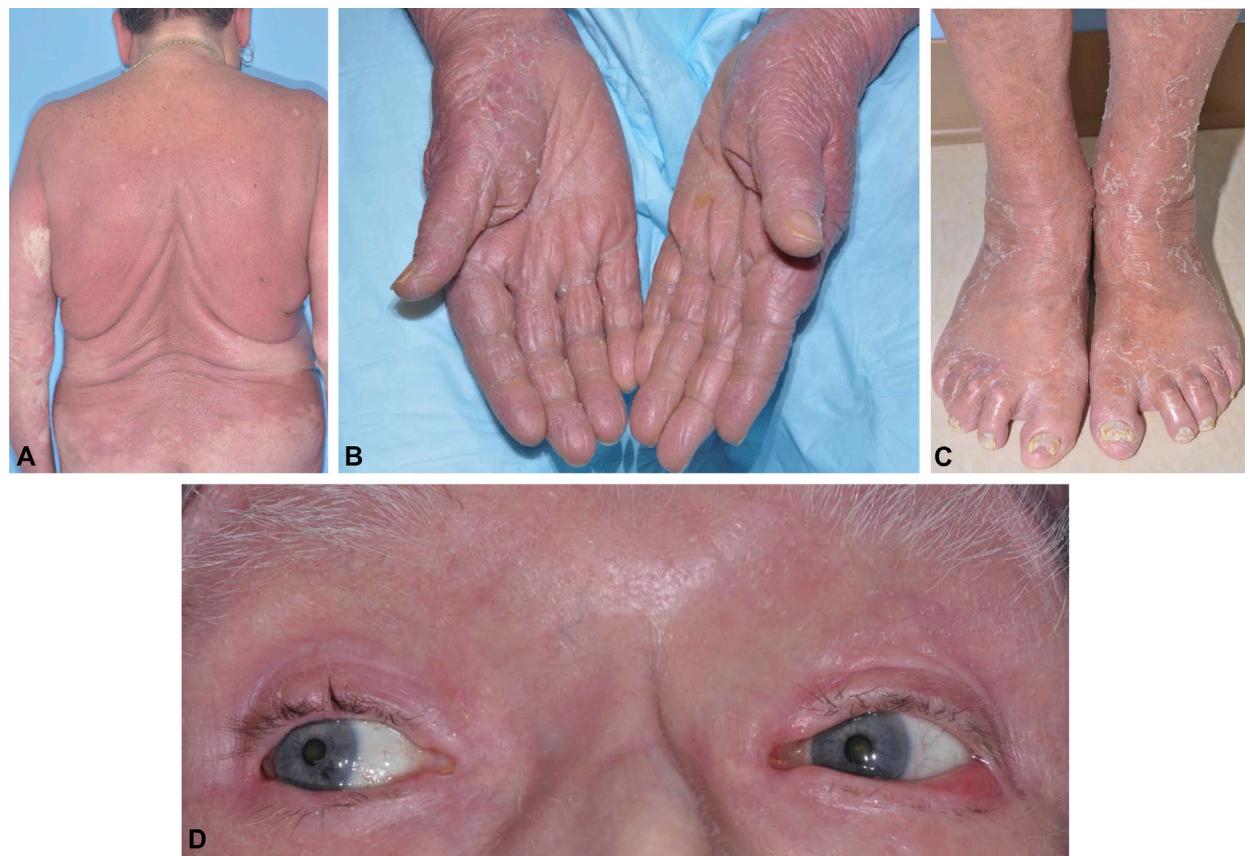


Fig 2. Sézary syndrome patient clinically presenting with generalized erythroderma (**A**) and scaling of the hands and feet with fissures on the palms and soles (**B** and **C**). Hair loss and eye changes such as ectropion are also seen (**D**).

dermatitis, psoriasis, and chronic photosensitivity reactions can all resemble E-CTCL.

HISTOPATHOLOGY

Key points

- **Classic mycosis fungoides is characterized by lymphocytes with cerebriform nuclei and a haloed appearance that display epidermotropism or populate the dermoepidermal junction**
- **Early mycosis fungoides may resemble chronic inflammatory dermatoses with reactive T lymphocytes and other immune cells**
- **Atypical T cells are CD4⁺CD45RO⁺ with frequent loss of T cell surface antigens, such as CD2, CD5, and/or CD7**
- **Circulating Sézary cells are characterized by a CD4⁺CD7⁻CD26⁻ phenotype**

Classic mycosis fungoides

MF consists of a proliferation of mature CD4⁺CD45RO⁺ memory T lymphocytes, with rare cases of CD8⁺ expression (often associated with

hypopigmented MF).^{34,35} The neoplastic infiltrate is comprised of predominantly small to intermediate-sized atypical lymphocytes with hyperchromatic, cerebriform nuclei surrounded by clear cytoplasm^{1,36} ("haloed" cells; Fig 3). The infiltrate in patches and plaques consists of a band-like lymphocytic infiltrate in the papillary dermis that may populate the dermoepidermal junction, variable numbers of inflammatory cells, and the epidermotropism of solitary cells or clusters of malignant lymphocytes (Pautrier microabscesses) in the absence of spongiosis is a clue to histopathologic diagnosis. Pautrier microabscesses are pathognomonic for MF, but are only seen in 25% of cases.^{1,36} Specific cytopathic changes, such as apoptotic keratinocytes, epidermal Civatte bodies, and dermal colloid bodies may also be present. In contrast, tumor lesions have deeper, dermal lymphocytic infiltrates with diminished or absent epidermotropism.

Early mycosis fungoides

A predominance of reactive lymphocytes and lack of cytologically atypical lymphocytes in initial biopsy

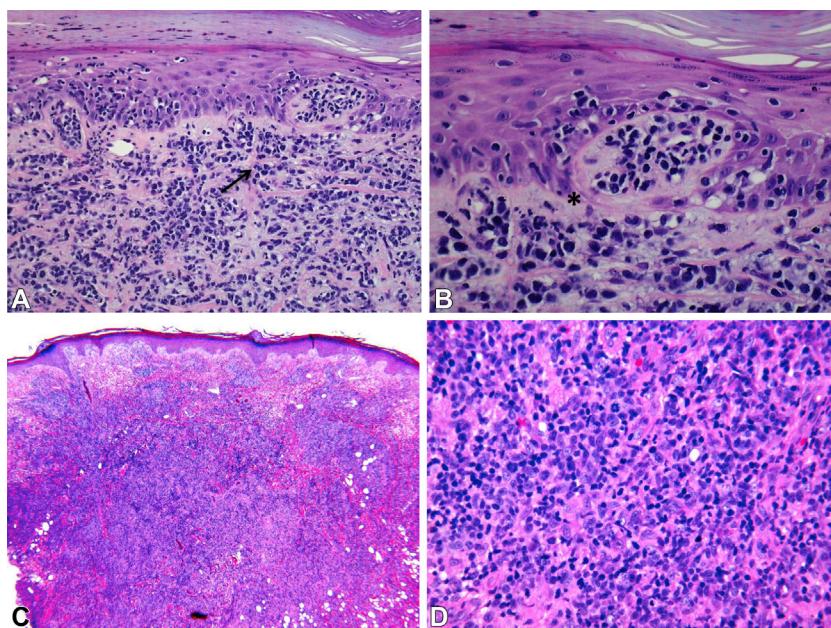


Fig 3. Mycosis fungoides. Plaque lesion with a band-like infiltrate of predominantly small to intermediate-sized atypical lymphocytes (**A**; arrow). The atypical lymphocytes are hyperchromatic with indented nuclei (cerebriform) with surrounding clear cytoplasm (haloed cells). Epidermotropism with Pautrier microabscesses are also seen (**B**; asterisk). **C** and **D**, A cutaneous tumor lesion presenting with dense, deep dermal infiltrate of atypical lymphocytes with the loss of epidermotropism. (Hematoxylin–eosin stain; original magnifications: **B** and **D**, $\times 200$; **C**, $\times 100$).

Table III. Algorithm for diagnosis of early mycosis fungoides proposed by the International Society for Cutaneous Lymphoma*

Criteria	Scoring system
Clinical	
Basic	2 points for basic plus 2 additional criteria
Persistent and/or progressive patches/thin plaques	
Additional	1 point for basic plus 1 additional criteria
Non–sun exposed location	
Size/shape variation	
Poikiloderma	
Histopathologic	
Basic	2 points for basic plus 2 additional criteria
Superficial lymphoid infiltrate	
Additional	1 point for basic plus 1 additional criteria
Epidermotropism without spongiosis	
Lymphoid atypia	
Molecular	
Clonal T cell receptor gene rearrangement	1 point for clonality
Immunopathologic	
$<50\%$ CD2 $^+$, CD3 $^+$, and/or CD5 $^+$ T cells	1 point for ≥ 1 criteria
$<10\%$ CD7 $^+$ T cells	
Epidermal/dermal discordance of CD2, CD3, CD5, or CD7	

A total of 4 points is required for the diagnosis of mycosis fungoides based on any combination of points from the clinical, histopathologic, molecular, and immunopathologic criteria.

*Adapted with permission from Pimpinelli et al.³⁹

specimens may resemble inflammatory skin diseases, confounding the diagnosis.³⁷⁻³⁹ As a result, concordance rates among pathologists are low for

the diagnosis of early MF, and serial biopsy specimens are needed from various clinical sites to render a definitive diagnosis.^{40,41}

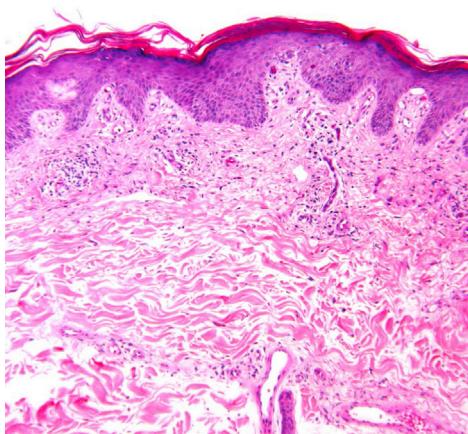


Fig 4. Sézary syndrome. Skin biopsy specimen revealing nonspecific histopathologic findings of a mild superficial perivascular lymphocytic infiltrate with scattered eosinophils. (Hematoxylin–eosin stain; original magnification: $\times 100$).

Since the 1970s, several studies have attempted to characterize the lymphocytic infiltrate in early MF.^{38,39,41-44} Guitart et al⁴⁵ created an integrated histologic criteria for early MF diagnosis based on the sequential evaluation of microscopic features: density of infiltrate with/without perivascular and dermal involvement, epidermotropism, and cellular atypia. Minor criteria includes reticular fibroplasia of the papillary dermis, intraepidermal atypical lymphocytes, and a lymphocytic infiltrate without inflammatory features. This system has now been implemented in clinical therapeutic trials as diagnostic criteria for MF. In addition, the ISCL proposed an algorithm for diagnosis of early MF that integrates clinical, histologic, immunophenotypic, and molecular criteria (Table III) and allows the diagnosis to be made in the absence of some of these features.³⁹

Erythrodermic mycosis fungoides/Sézary syndrome

Histopathologic features of EMF and SS are variable (Fig 4), with less prominent features, such as epidermotropism, Pautrier microabscesses, and haloed lymphocytes.^{36,46} Studies have shown a variable pattern of dermal lymphocytes from superficial perivascular to dense lichenoid infiltrate, suggesting that the features of EMF/SS may be more subtle than patch or plaque MF⁴⁷ (Fig 5).

Immunophenotyping

MF is characterized by the presence of CD3⁺ T cell lymphocytes that express a T cell helper phenotype

(CD4⁺), with rare cases of CD8⁺ cytotoxic/suppressor T cell immunophenotype.⁴⁸⁻⁵² An elevated CD4:CD8 ratio (≥ 6) is often seen, but a normal or decreased ratio does not exclude a diagnosis of MF.⁵³ These cells also express CD45RO, a marker of mature memory T cells.⁵⁴ The loss of T cell surface antigens, such as CD2, CD5, and CD7, is a common phenotypic aberration that may be associated with disease progression.⁵⁵ The loss of CD7 in particular is considered a sensitive and specific finding for MF.^{48,52,55-58}

The detection and quantification of Sézary cells for the diagnosis of SS and MF with leukemic involvement has traditionally been determined by their morphologic identification on peripheral blood smears. This has largely been replaced by flow cytometry because of high interobserver variability in cell counts.⁵⁹ In addition, atypical lymphocytes with cerebriform nuclei can be found in the blood of healthy individuals and those with benign inflammatory skin diseases. Flow cytometry identifies neoplastic T cells, which are characterized as CD4⁺CD7⁻ and/or CD4⁺CD26⁻.^{60,61} However, subsets of CD7⁻CD26⁻ T cells can also be seen in benign inflammatory dermatoses.⁶²⁻⁶⁴

T cell clonality

The identification of dominant T cell clones in the skin is a confirmatory diagnostic test, and is determined by detection of alfa/beta or gamma/delta T-cell receptor (TCR) gene rearrangements.⁶⁵ Clonality has been reported in 40% to 90% of MF cases, with gamma and beta TCR gene rearrangements most commonly identified.⁶⁶⁻⁷⁰ Southern blot techniques were used in the past, but recent studies have shown that polymerase chain reaction using the BIOMED-2 method detect gene rearrangements with higher sensitivity (80-90%) and specificity (>90%).^{66,68}

Clonality may be stage-dependent and is seen in about 50% of patch, 73% of plaque, and 83% to 100% of tumor MF and EMF.⁵⁵ In early MF lesions with small neoplastic cell populations, clonality may be difficult to determine. The prognostic significance of clonality is also unclear, particularly in early MF, although the presence of a peripheral blood clone in early MF may portend a poorer clinical course.^{71,72} Delfau-Larue et al^{67,73} suggested its utility in monitoring treatment response and the detection of residual disease. However, dominant T cell clones have also been detected in 25% to 65% of patients with benign inflammatory dermatoses,⁷⁴⁻⁷⁷ although the detection of the same T cell clone in different biopsy specimens is more supportive of MF.⁶⁹ Identification of the same clone in multiple skin and/or lymph node

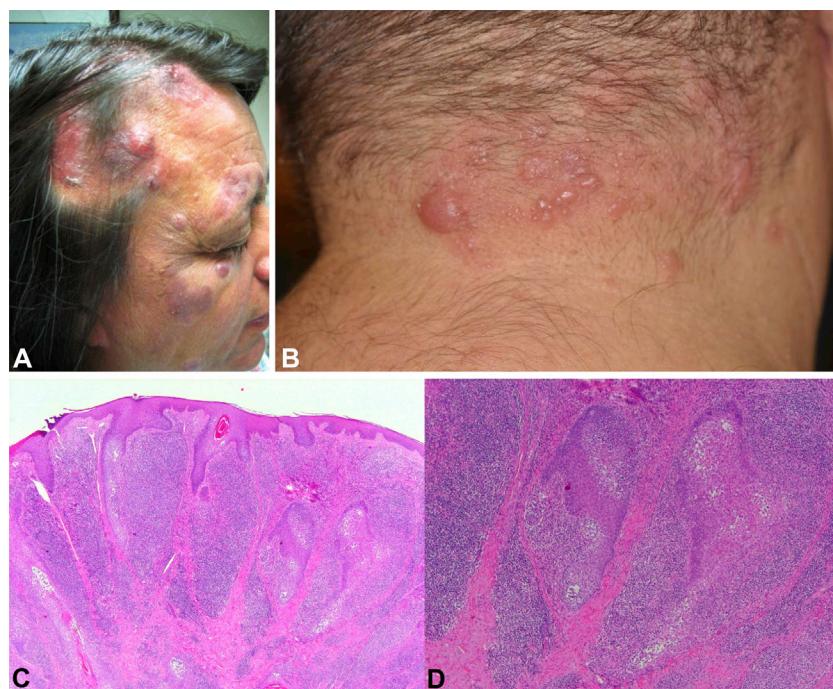


Fig 5. Folliculotropic mycosis fungoides patients clinically presenting with plaques and tumors with associated alopecia on the face and forehead, including the eyebrows and scalp (**A**) and erythematous perifollicular and follicular papules and pustules on the occipital area (**B**). **C** and **D**, The atypical lymphoid infiltrate is characterized by a dense, deep dermal and perifollicular infiltrate with folliculotropism and mucin deposition. (Hematoxylin–eosin stain; original magnifications: **C**, $\times 100$; **D**, $\times 200$).

biopsy specimens is also more associated with progressive disease than identification of oligoclonal or multiclonal T cell populations.⁷⁸

The emergence of a dominant T cell clone in MF is at the expense of the reactive T cell population. It was previously believed that a malignant monoclonal T cell proliferation developed against a reactive polyclonal T cell background. Yawalkar et al⁶⁵ found that there is malignant T cell clonal expansion with decreased normal T cells, resulting in a reduction in overall T cell repertoire complexity. This loss creates a relative lymphopenia that may play a role in the immunosuppression seen in patients with advanced disease. Another study suggested that CTCL evolves from a multilineage progression of genetically unstable subclones into a stable clone that subsequently proliferates into the neoplastic T cell population that defines MF.⁷⁹

PATHOGENESIS OF MYCOSIS FUNGOIDES AND SÉZARY SYNDROME

Key points

- The skin microenvironment plays a crucial supporting role in the development of mycosis fungoides

- Skin homing of malignant T cells involves chemokines, cytokines, and adhesion molecules that participate in lymphocyte extravasation and migration to the skin
- $T_{H}1$ cytokines predominate in early mycosis fungoides, and $T_{H}2$ cytokines in advanced mycosis fungoides/Sézary syndrome
- Recent studies have suggested that mycosis fungoides and Sézary syndrome arise from different memory T cell subsets

Tumor microenvironment

The skin microenvironment plays a crucial supporting role in the development of MF. MF is presumed to arise from a background of chronic inflammation; in addition to dendritic cells, several other immune cells, including reactive T cells, macrophages, mast cells, and plasma cells have been identified. High numbers of reactive CD8⁺ cytotoxic T cells are found in early skin lesions, likely secondary to dendritic cell recruitment, and may contribute to an antitumor response.^{80,81} FOXP3⁺ regulatory T cells (Treg) are also present and have been correlated with improved survival, presumably via suppression of malignant cell proliferation.⁸² Both Treg and cytotoxic T cells are significantly decreased in advanced

plaque and tumor lesions. Studies have shown that malignant T cells in advanced MF and SS actually express a regulatory and cytotoxic T cell phenotype, which may lead to a decreased immune response and apoptosis of the surrounding immune cells.^{83,84}

Macrophages may secrete chemokines that have an immunomodulatory effect and contribute to lesional lymphocyte containment, although other studies have suggested that increased lesional macrophages are associated with tumor growth and disease progression.⁸⁵⁻⁸⁷ Studies have also shown that mast cells serve as critical regulators of the tumor microenvironment, and a protumorigenic role in cutaneous lymphomas was recently established.⁸⁸

Skin homing of malignant T cells

The skin homing mechanism of malignant T cells is not completely elucidated, although the role of adhesion molecules and chemokines has been hypothesized. Data have shown that skin homing T cells isolated from patients with MF/SS express cutaneous lymphocyte antigen (CLA) and the chemokine receptors CCR-4 and CCR-10, which bind to their corresponding skin-derived ligands on endothelial cells, keratinocytes, and/or Langerhans cells, thereby facilitating migration into the dermis and epidermis.⁸⁹⁻⁹⁴ The profile of chemokine receptors changes with disease progression, with neoplastic cells increasingly expressing lymphatic homing CCR7 in tumor stage MF, correlating with a loss of epidermotropism and the potential for extracutaneous involvement.⁹⁵

Interestingly, there is also a change in cytokine expression profile with disease progression. T_H1 cytokines, interferon gamma, and interleukins (ILs-12 and -2) predominate in early MF.⁹⁶ In advanced MF and SS, a shift from T_H1 to T_H2 cytokines is seen.^{97,98} T_H2 cytokines (ILs-4, -5, -10, and -13) have been correlated with eosinophilia, erythroderma, high levels of immunoglobulin E, immunosuppression, and increased susceptibility to bacterial infections seen in advanced MF/SS. Recent studies have also shown that MF and SS arise from different memory T cell subsets^{99,100}—malignant T cells of SS are of the central memory T cell subset that are capable of circulating between skin, the lymph nodes, and blood; those in MF were comprised of nonrecirculating skin resident effector memory T cells.

GENETIC, CHROMOSOMAL, AND MOLECULAR FINDINGS

Key points

- Defective apoptosis primarily through impaired Fas-mediated apoptosis is thought to play a crucial role in pathogenesis

- The isolation of specific microRNAs from patients with mycosis fungoides may help distinguish cutaneous T-cell lymphoma from benign skin diseases
- Programmed-Death-1 may have diagnostic value in differentiating Sézary syndrome from mycosis fungoides

Genetic and chromosomal abnormalities

The pathogenesis of MF/SS is characterized by an altered immune biology and the accumulation of cytogenetic abnormalities during disease progression, including increased transcription factor activity, such as amplification of JUNB, that is involved in T-cell proliferation, differentiation, and apoptosis.¹⁰¹⁻¹⁰³ Similarly, constitutive activation of STAT3 transcription factor is seen in advanced/tumor MF and is a proposed therapeutic target.^{104,105} Dysregulated cell cycle control has also been identified, including the decreased expression of regulating proteins p14, p15, and p16, which are able to interact with cyclin-dependent kinases and induce cell cycle arrest.¹⁰⁶⁻¹⁰⁸ Hemi- or homozygous deletion of the encoding locus CDKN2A-CDKN2B on chromosome 9p21 or aberrant CpG island methylation leading to epigenetic silencing have been seen in both early and late stage MF.^{109,110} Additional abnormalities include allelic losses on chromosomes 10q and 17p and microsatellite instability, although their clinical relevance and prognostic significance are still unclear.^{111,112}

Dysfunctional apoptosis

Defective apoptosis leading to apoptosis resistance has been identified as a central feature in MF. Apoptosis is partly mediated by death receptors, notably Fas, which is part of the tumor necrosis factor family of receptors. Decreased and/or defective Fas expression by neoplastic T cells has been associated with advanced/aggressive disease and impaired Fas-mediated apoptosis.¹¹³⁻¹¹⁶ Multiple mechanisms, including Fas gene mutations,¹¹⁴ promoter hypermethylation,¹¹⁷ and the production of nonfunctioning splice variants have been reported,¹¹⁸ enabling continued neoplastic T cell proliferation. Malignant T cells may also aberrantly express cFLIP, an intracellular inhibitor of death-receptor mediated apoptosis, further contributing to the resistance of Fas ligand signaling.¹¹³

Molecular findings

MicroRNAs are small noncoding RNAs that regulate gene expression. A recent study has shown the potential of microRNA analyses to differentiate CTCL from benign skin disorders, suggesting its diagnostic potential. A microarray screen found that 5 microRNAs

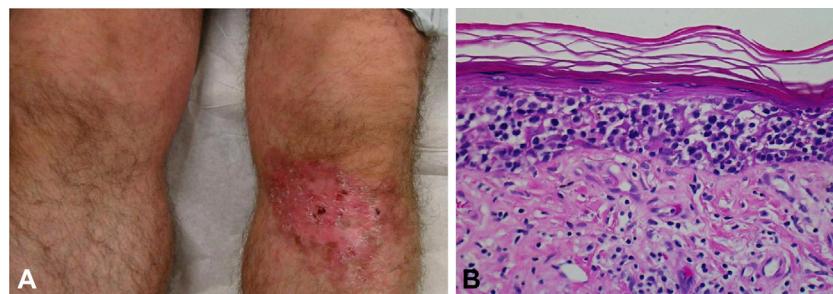


Fig 6. Pagetoid reticulosis. Patient presenting with a solitary scaly plaque on left knee (**A**). There is marked epidermotropism of atypical lymphocytes (**B**). (Hematoxylin–eosin stain; original magnification: **B**, $\times 200$).

(miRs-203, -205, -326, -663, and -711) identify CTCL from benign skin diseases with >90% accuracy.¹¹⁹

A membrane molecule that belongs to the CD28/CTLA-1 receptor family, Programmed-Death-1 (PD-1), may have utility in the identification of SS. Engagement of PD-1 on T cells with its ligand has been shown to inhibit T cell activation and proliferation. Recent studies have shown a high expression of PD-1 by neoplastic T cells in SS but not MF.^{120,121} Samimi et al¹²¹ found a decrease in PD-1 expression with treatment, suggesting its potential as a marker for monitoring treatment response in SS. The clinical significance of high PD-1 expression in SS is unclear, although it may contribute to the profound immunosuppression seen in SS.

MYCOSIS FUNGOIDES SUBTYPES AND VARIANTS

Key points

- Folliculotropic mycosis fungoides, granulomatous slack skin, and pagetoid reticulosis are well recognized subtypes of mycosis fungoides, although numerous variants exist
- Folliculotropic mycosis fungoides is the most common mycosis fungoides variant, marked by an aggressive course with a predilection for hair follicles in the head and neck region
- Granulomatous features are seen in 2% of cutaneous lymphoma, with 2 distinct entities recognized: granulomatous slack skin and granulomatous mycosis fungoides
- Large cell transformation is characterized by the presence of large T cell lymphocytes and is generally associated with disease progression and a poorer prognosis

Folliculotropic mycosis fungoides

Folliculotropic MF is the most common MF variant. It can present as plaques, acneiform lesions, comedones, cysts, and nodular prurigo-like lesions

surrounding hair follicles, involving the head with typical eyebrow involvement (Fig 5). Associated scarring and alopecia are often seen.³⁰ Patients with folliculotropic MF experience significant pruritus. Characteristic histopathologic features include a perifollicular lymphocytic infiltrate with epidermal sparing.¹²² Follicular destruction with or without mucinous degeneration can also be seen.¹²³ Folliculotropic MF is generally marked by a more aggressive course with a poorer prognosis.

Pagetoid reticulosis

Pagetoid reticulosis, also called Woringer–Kolopp disease, is an indolent MF variant that presents with solitary or localized scaling patches or plaques typically found on the distal extremities^{1,124} (Fig 6). The pathologic hallmark is epidermotropic lymphocytes that appear as pagetoid cells, either singly or in clusters in the epidermis, with prominent epidermal hyperplasia.³⁶ The majority of these cells are characterized by a CD4⁺ T cell helper phenotype, although CD8⁺ cytotoxic/suppressor T cell and the CD4⁻CD8⁻ phenotype have also been reported.¹²⁴

Granulomatous mycosis fungoides and granulomatous slack skin

In general, granulomatous features are seen in approximately 2% of cutaneous lymphomas.^{125,126} Various histopathologic patterns, including epithelioid/sarcoidal, tuberculoid, periadnexal, and granuloma annulare-like granulomas are seen in granulomatous MF (GMF).¹²⁶ The granulomatous component may mask the lymphoid infiltrate, leading to a delay in diagnosis. Epidermotropism and clonal TCR gene rearrangements may help confirm the diagnosis.¹²⁷ Clinically, GMF resembles mostly classic MF (Fig 7). Recent studies have shown that GMF is associated with an increased disease progression and poorer prognosis compared to classic MF.^{127,128}



Fig 7. Granulomatous mycosis fungoides. **A** and **B**, Note the hyperkeratotic plaques with raised borders mimicking granuloma annulare-like plaques. **C** and **D**, The histopathologic findings of the skin biopsy specimen reveal perivascular granulomas with atypical lymphocytes. (Hematoxylin–eosin stain; original magnifications: **C**, $\times 100$; **D**, $\times 200$).

Granulomatous slack skin presents with patches and plaques in intertriginous areas with the development of pendulous/lax skin folds¹²⁸ (Fig 8). In addition to multinucleated giant cells and granulomatous infiltrate, granulomatous slack skin is characterized by prominent elastolysis on pathology along with phagocytosis of lymphocytes and elastic fibers. Both GMF and granulomatous slack skin have been associated with the development of secondary lymphoid neoplasias, in particular Hodgkin lymphomas.^{1,128}

Transformed mycosis fungoides

Large cell transformation (LCT) is characterized by a morphologic change of small to medium-sized atypical T cell lymphocytes to a large cell variant (Fig 9). The presence of large lymphocytes as >25% of the total cell population in skin or lymph nodes is considered diagnostic. LCT is generally associated with disease progression, but can present as an initial manifestation of MF; 1.4% of patients with stage I disease developed LCT in contrast to 25% and 50% of stage IIB and IV patients, respectively.¹²⁹ A recent study on prognostic factors in 100 patients with LCT found a median survival of 24 months (range, 1-235 months), with a 5-year disease-specific survival and overall survival of 38% and 33%, respectively.¹³⁰ These results are similar to previous studies, with

median survivals ranging from 12 to 36 months and 5-year OS ranging from 11% to 32%. Transformed MF at the time of the initial diagnosis may carry a better prognosis compared to transformed MF cases diagnosed late in the disease course.^{130,131} Poor prognostic factors in LCT include advanced clinical stage at time of transformation, early onset of transformation (<2 years from the time of MF diagnosis), extracutaneous sites of transformation, and elevated beta-2-microglobulin and lactate dehydrogenase.^{131,132} The percentage of large cells (>25%) did not have any effect on prognosis.

LCT has classically been described as occurring within MF tumor lesions. A recent study identified 3 clinical patterns of LCT in MF patients: (1) a new solitary nodule within a long standing classic MF patch/plaque, (2) the abrupt onset of multiple nodules that persist, and (3) a new or enlarging tumor.¹³³ It is often advised to obtain biopsy specimens from patients with established disease who develop new papules, plaques, or tumors in order to rule out LCT.

The diagnosis of MF, particularly in the early phases, may be difficult, with nonspecific histologic findings confounding the clinicopathologic diagnosis. Significant strides have been made in facilitating early MF diagnosis using immunophenotyping and

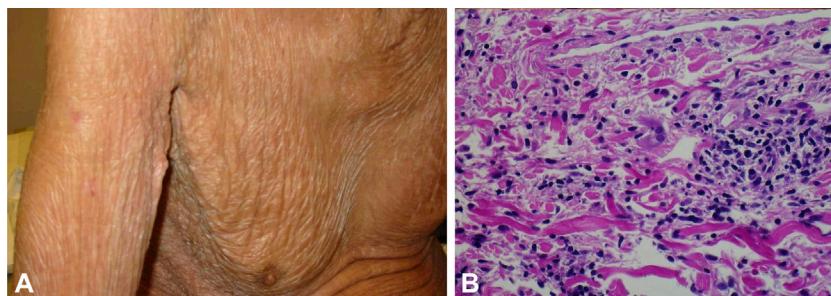


Fig 8. Granulomatous slack skin. **A**, Pendulous lax skin folds. **B**, Classic pathology findings of multinucleated giant cells with elastophagocytosis and an atypical dermal lymphocytic infiltrate. (Hematoxylin–eosin stain; original magnification: **B**, $\times 200$).

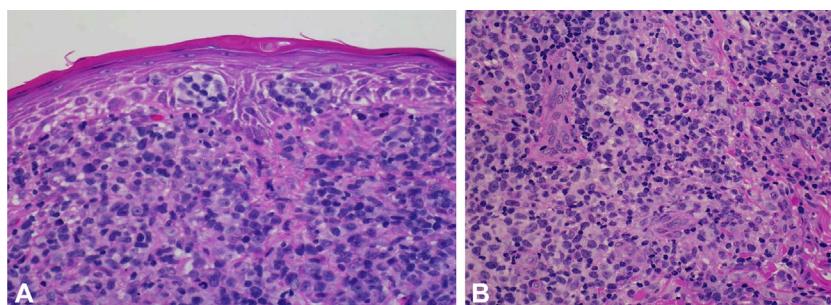


Fig 9. Mycosis fungoides with large cell transformation. Skin biopsy specimen with histopathologic findings (**A** and **B**) of large atypical lymphocytes making up approximately 50% of the infiltrate. The histopathologic findings are consistent with large cell transformation. (Hematoxylin–eosin stain; original magnifications: **A**, $\times 100$; **B**, $\times 200$).

molecular analyses for TCR gene rearrangement studies. A recent study has shown the potential of microRNA analyses to differentiate CTCL from benign skin disorders. In addition, current research suggests that MF and SS may arise from different T cell subsets and express different molecules (ie, PD-1) and therefore constitute different entities. This understanding of distinct subsets suggests the potential for tailored therapeutic strategies for MF and SS.

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Primary cutaneous T-cell lymphoma (mycosis fungoides and Sézary syndrome)

Part II. Prognosis, management, and future directions

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After completing this learning activity, participants should be able to identify topical and skin-directed therapy for patch, plaque, and tumor stage MF; demonstrate a fundamental understanding of systemic treatment options in tumor stage MF/

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Both mycosis fungoides (MF) and Sézary syndrome (SS) have a chronic, relapsing course, with patients frequently undergoing multiple, consecutive therapies. Treatment is aimed at the clearance of skin disease, the minimization of recurrence, the prevention of disease progression, and the preservation of quality of life. Other important considerations are symptom severity, including pruritus and patient age/comorbidities. In general, for limited patch and plaque disease, patients have excellent prognosis on ≥ 1 topical formulations, including topical corticosteroids and nitrogen mustard, with widespread patch/plaque disease often requiring phototherapy. In refractory early stage MF, transformed MF, and folliculotropic MF, a combination of skin-directed therapy plus low-dose immunomodulators (eg, interferon or bexarotene) may be effective. Patients with advanced and erythrodermic MF/SS can have profound immunosuppression, with treatments targeting tumor cells aimed for immune reconstitution. Biologic agents or targeted therapies either alone or in combination—including immunomodulators and histone-deacetylase inhibitors—are tried first, with more immunosuppressive therapies, such as alemtuzumab or chemotherapy, being generally reserved for refractory or rapidly progressive disease or extensive lymph node and metastatic involvement. Recently, an increased understanding of the pathogenesis of MF and SS with identification of important molecular markers has led to the development of new targeted therapies that are currently being explored in clinical trials in advanced MF and SS. (J Am Acad Dermatol 2014;70:223.e1-17.)

Key words: cutaneous T-cell lymphoma; immunomodulators; mycosis fungoides; phototherapy; prognosis; Sézary syndrome; skin-directed treatment; staging; systemic treatment; targeted therapies; topical corticosteroids; topical nitrogen mustard; topical retinoids/rexinoids.

The treatment of mycosis fungoides (MF) and Sézary syndrome (SS) is primarily determined by disease extent and the impact on quality of life, prognostic factors (eg, folliculotropic MF and large cell transformation), and patient age/comorbidities. Early stage MF (stages IA-IIA), with disease primarily confined to the skin, has a favorable prognosis, with skin-directed therapies as first-line treatment. Prolonged complete remissions have been obtained, although disease cure is unclear.

Advanced stage MF/SS (stages IIB-IVB) is often treatment refractory and results in an unfavorable prognosis; treatment is aimed at reducing the tumor burden, delaying disease progression, and preserving quality of life. Current approaches include immunobiologic and targeted therapies, but the duration of clinical response is often short. Single/multiagent chemotherapy should be reserved for cases that are refractory to treatment. The revised guidelines by the International Society for Cutaneous Lymphomas (ISCL), the United States Cutaneous Lymphoma Consortium (USCLC), and the Cutaneous Lymphoma Task Force of the European Organization of Research and Treatment of Cancer (EORTC) include treatment options for MF/SS that match the National Comprehensive

Abbreviations used:

BSA:	body surface area
CR:	complete response
CRR:	complete response rate
CTCL:	cutaneous T-cell lymphoma
ECP:	extracorporeal photopheresis
EORTC:	European Organization of Research and Treatment of Cancer
HDACi:	histone deacetylase inhibitor
IFN α :	interferon-alfa
ISCL:	International Society for Cutaneous Lymphoma
MF:	mymcosis fungoides
mSWAT:	modified severity-weighted assessment tool
NBUVB:	narrowband ultraviolet B light
NCCN:	National Comprehensive Cancer Network
NK:	natural killer
NM:	nitrogen mustard
NMSC:	nonmelanoma skin cancer
ORR:	overall response rate
PUVA:	psoralen plus ultraviolet A light phototherapy
RAR:	retinoic acid receptor
RXR:	retinoid X receptor
SS:	Sézary syndrome
TNMB:	tumor, node, metastasis, blood
TSEBT:	total skin electron beam therapy
USCLC:	United States Cutaneous Lymphoma Consortium
UVB:	ultraviolet B light

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Cancer Network (NCCN) guidelines for MF/SS in 2010.¹ This review focuses on the staging, prognosis, and management of MF/SS, with an emphasis on the development of new treatment strategies. Of note, the response rate and duration data come from a range of studies with variable inclusion criteria, making it difficult to compare the efficacy of different treatments. Therefore, efforts have been made by the ISCL, USCLC, and EORTC to standardize both clinical end points and response criteria.²

EVALUATION OF A PATIENT, STAGING, PROGNOSIS

Key points

- Patient evaluation requires a multidisciplinary team approach with dermatologists, oncologists, dermatopathologists, and radiation oncologists
- Staging of a patient requires an assessment of skin, lymph node, viscera, and blood involvement
- The prognosis of mycosis fungoides in most patients with limited patch/plaque disease is favorable and similar to that of an age-, sex-, and race-matched control population

Initial work-up

MF/SS patients should ideally be assessed by a multidisciplinary cutaneous T-cell lymphoma (CTCL) team of dermatologists and oncologists, with support from radiation oncologists, pathologists, and clinical psychologists. A routine evaluation includes a complete physical examination with a formal estimation of skin tumor burden using a modified severity-weighted assessment tool (mSWAT), measuring the total body surface area (BSA) by using the patient's palm and fingers to represent 1% BSA. Patch, plaque, and tumor BSA are determined separately and multiplied by a factor (1, 2, and 4, respectively) to generate the standardized mSWAT score² (Fig 1).

Diagnostic tests, including a complete blood cell count with differential, chemistry panel, lactate dehydrogenase, and a skin biopsy specimen for histology, immunophenotyping, and T cell receptor gene rearrangement studies should be performed at a CTCL referral center. Sézary cell count, circulating T cell subsets and clonality, positron emission tomography/computed tomography scans, and/or lymph node biopsy specimens should be obtained in cases suggestive of lymphadenopathy and/or systemic disease to establish staging, with HIV and human T-lymphotrophic virus type 1 serology testing in select patients.³

Staging and prognosis

Accurate staging in MF/SS is essential to determine treatment and prognosis. MF/SS staging relies on the tumor, node, metastasis, blood (TNMB) classification proposed by the Mycosis Fungoïdes Cooperative Group and revised by the ISCL/EORTC, which considers the extent of skin involvement (T), presence of lymph node (N), visceral disease (M), and detection of Sézary cells in the peripheral blood (B); this information is translated into a clinical stage^{4,5} (Tables I and II).

Most MF patients (~70%) have early stage disease (stage IA-IIA) at the time of the initial diagnosis.⁶ The extent of cutaneous involvement (ranging from T1-T4) is significantly associated with a prognosis with decreased overall survival, and progression-free survival in advanced T-stage. One large study found that the risk for disease progression at 5 years was 10% in T1, 22% in T2, and 48% to 56% in T3 to T4 levels of cutaneous involvement.⁷

Patients with stage-IA MF have a similar life expectancy as age-, sex-, and race-matched control populations.⁸ Inferior survival has been shown in plaque over patch disease for both limited (T1) and extensive (T2) skin disease.⁹ Other prognostic factors include advanced age at diagnosis, elevated lactate dehydrogenase and beta-2-microglobulin levels, large cell transformation, and folliculotropic MF.^{6,7,9-11} A high Sézary cell count, the loss of T cell markers (eg, CD5 and CD7), and chromosomal abnormalities in circulating T cells are also independently associated with a poor outcome.² The presence of a T cell clone in the peripheral blood in B0 patients (<5% Sézary cells) and identical clones in blood and skin portend a poorer prognosis.^{9,12}

SKIN-DIRECTED THERAPIES

Key points

- Topical corticosteroids are the most common treatment used in early mycosis fungoides and serve as an adjunct to other topical and systemic therapies at all stages
- Topical nitrogen mustard and phototherapy have similar efficacy in early stage mycosis fungoides with maintenance therapy needed for prolonged complete remissions
- Total skin electron beam therapy at a standard dose (30 Gy) is an effective treatment in refractory/relapsed extensive plaque and tumor mycosis fungoides associated with significant skin toxicity
- Low-dose local radiation therapy may be useful in selected lesions

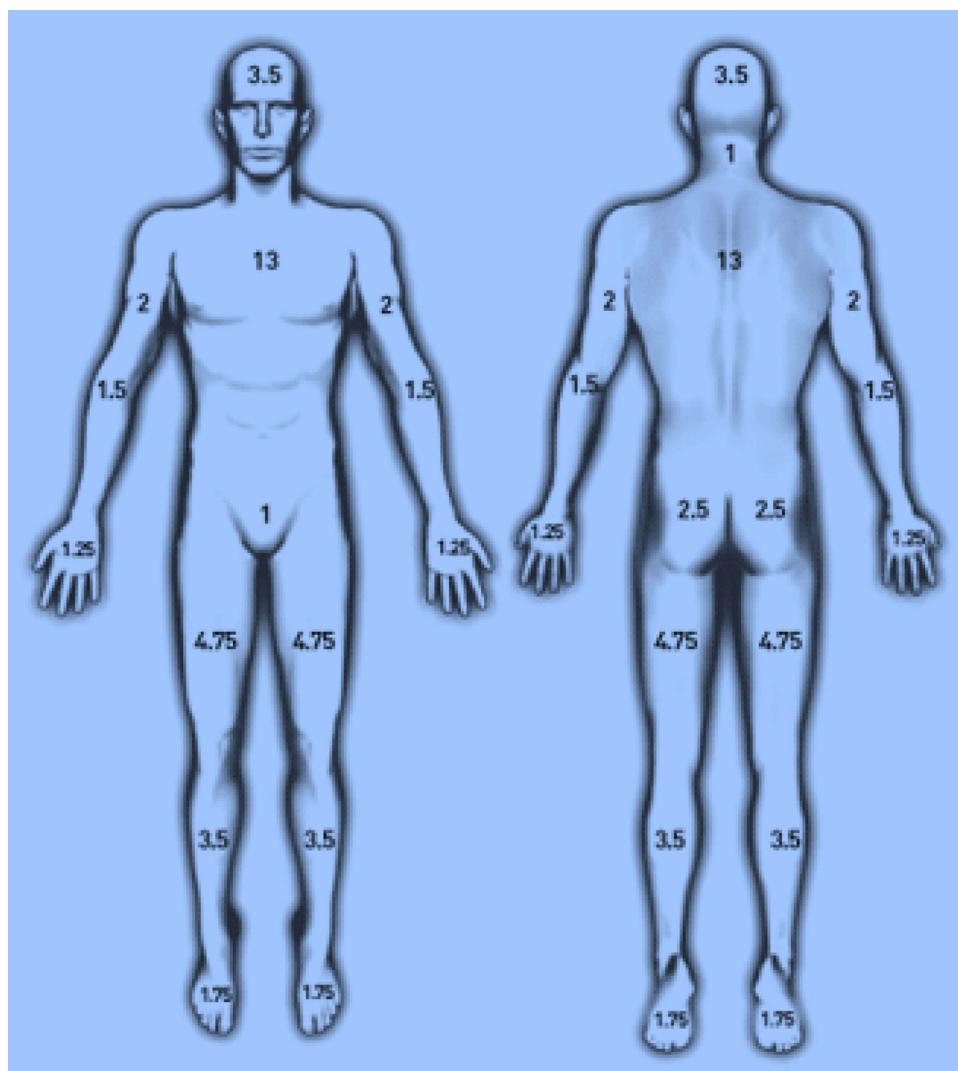


Fig 1. Modified severity-weighted assessment tool (mSWAT) adapted from Levenson and Lund.²¹¹

Topical corticosteroids

Corticosteroids are frequently used in early MF and as adjunctive therapy in more advanced stages of the disease (Table III). Their multiple effects include induction of apoptosis, impact on lymphocyte adhesion to endothelium, and the downregulation of transcription factors (nuclear factor- κ B and activator protein-1) with decreased cytokine, adhesion molecule, and growth factor production.¹³⁻¹⁶ Early studies found overall response rates (ORRs) between 80% and 90%,¹⁷⁻²⁰; a large prospective study of 79 patients with patch disease (stage T1/T2) on daily topical class I to III steroids (median observation time, 9 months) found that 32 (63%) of T1 patients and 7 (25%) of T2 patients achieved a complete response (CR).²¹ A sustained response was not seen after steroid discontinuation.²¹ Topical steroids also decrease erythema, scaling, and pruritus in

erythrodermic CTCL.¹⁶ Side effects associated with long-term use include skin atrophy, hypopigmentation, striae, and potential systemic absorption. The latter was observed in 13% of patients in 1 study without adrenal suppressive effects.²¹

Topical nitrogen mustard (mechlorethamine hydrochloride)

Nitrogen mustard (NM) is an alkylating agent. Topical NM applications are commonly used for early stage MF. NM-induced DNA damage results in its systemic anticancer effects, but the topical formulation may work via immune mechanisms affecting keratinocyte–Langerhans cell–T cell interactions.²²

Efficacy at concentrations of 0.01% to 0.02% in an aqueous solution or ointment base has been well reported, with a CR in up to 72% of early stage MF patients and occasional long-term remissions

Table I. Revisions to the tumor, node, metastasis, blood classification of mycosis fungoides/Sézary syndrome proposed by the International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer*

TNMB stages	Stage description
Skin (T)	
T1	Limited patches, papules, and/or plaques (<10% BSA)
T1a	Patches only
T1b	Presence of plaques with or without patches
T2	Patches, papules, or plaques covering ≥ 10% BSA
T2a	Patch only
T2b	Presence of plaques with or without patches
T3	≥ 1 tumors (≥ 1 cm in diameter)
T4	Generalized erythroderma (≥ 80% BSA)
Node (N)	
N0	No clinically abnormal (palpable; ≥ 1.5 cm diameter) peripheral LNs
N1	Clinically abnormal LNs; histopathology Dutch grade 1 or NCI LN ₀₋₂
N1a	Clone positive
N1b	Clone negative
N2	Clinically abnormal LNs; histopathology Dutch grade 2 or NCI LN ₃
N2a	Clone negative
N2b	Clone positive
N3	Clinically abnormal LNs; histopathology Dutch grade 3-4 of NCI LN ₄ ; clone positive OR negative
Visceral (M)	
M0	No visceral organ involvement
M1	Visceral involvement (pathology confirmation of specific organ involved)
Blood (B)	
B0	Absence of significant blood involvement (≤ 5% of peripheral blood lymphocytes are atypical/Sézary cells)
B0a	Clone negative
B0b	Clone positive (same clone as in skin)
B1	Low blood tumor burden (>5% of peripheral blood lymphocytes are atypical/Sézary cells but does not meet criteria of B2)
B1a	Clone negative
B1b	Clone positive
B2	High blood tumor burden defined as one of the following: ≥ 1000 Sézary cells/μL with positive clonal rearrangement of TCR; CD4:CD8 ratio ≥ 10 with positive clone; or CD4 ⁺ CD7 ⁻ cells ≥ 40% or CD4 ⁺ CD26 ⁻ cells ≥ 30% with positive clone

BSA, Body surface area; LN, lymph node; NCI, National Cancer Institute; TCR, T-cell receptor; TNMB, tumor, node, metastasis, blood.

*Adapted with permission from Olsen et al.⁵

(>8 years).²³⁻²⁸ A recent multicenter trial of a 0.02% gel formulation resulted in similar efficacy that has led to the approval in 2013 by the US Food and Drug Administration for the treatment of stage IA/IB MF patients with previous skin-directed therapy.²⁹ However, only 11% maintained a CR after 10 years.^{26,27} In 1 study on 203 stage I to III MF patients, CR rates (CRRs) of 76% to 80% in stage IA and 35% to 68% for stage IB patients were observed.²² Skin clearance may require ≥ 6 months and is usually followed by maintenance therapy, although there is no evidence that prolonged maintenance reduces recurrence.³⁰

Cutaneous side effects are common, including burning, pruritus, and irritant or allergic contact dermatitis, the latter being much more common in aqueous formulations; topical corticosteroids may be helpful.³¹ There is a small increased risk (1-5%) of

developing nonmelanoma skin cancers (NMSCs), especially with concomitant radiation and psoralen plus ultraviolet A light phototherapy (PUVA).^{22,30}

Topical retinoids

Bexarotene is a synthetic retinoid (rexinoid) with the oral form selectively binding retinoid X receptor (RXR) isoforms, affecting cell differentiation and inducing apoptosis.^{32,33} The mechanism of action of topical bexarotene 1% gel, which is approved by the US Food and Drug Administration for the treatment of early stage MF (up to 4 times daily), is less clear. Topical bexarotene is recommended twice daily; high rates of irritation are seen with 4 times/day application. Responses were seen in most patients (stage IA-IIA) after a median of 20 weeks of treatment (ORR, 63%; CR, 21%).³⁴ Tazarotene is a

Table II. Revisions to the staging of mycosis fungoides and Sézary syndrome based on International Society for Cutaneous Lymphomas and the European Organization of Research and Treatment of Cancer revisions to the tumor, node, metastasis, blood classification⁵

Stage	T	N	M	B
IA	1	0	0	0 or 1
IB	2	0	0	0 or 1
IIA	1 or 2	1 or 2	0	0 or 1
IIB	3	0-2	0	0 or 1
IIIA	4	0-2	0	0
IIIB	4	0-2	0	1
IVA ₁	1-4	0-2	0	2
IVA ₂	1-4	3	0	0-2
IVB	1-4	0-3	1	0-2

B, Blood; M, metastasis; N, node; T, tumor.

topical retinoid that acts at the retinoic acid receptor (RAR). It was found to induce response in 58% of patients with limited (<20% skin involvement) or stable/refractory patch or plaque disease. Both topical bexarotene and 0.1% tazarotene gel cause local irritation.³⁵

Phototherapy

PUVA has an established benefit in early stage MF and involves oral 8-methoxysoralen, which sensitizes the skin to ultraviolet A light radiation (320-400 nm), inducing tumor cell apoptosis and DNA damage, suppressing keratinocyte cytokine production, and depleting Langerhans cells.³⁶⁻³⁸

The initial ultraviolet A light dosage is approximately 0.5 J/cm², increasing as tolerated, and given 3 times weekly until CR is achieved. Proper eye protection is needed for 12 to 24 hours after treatment sessions for cataract prevention. Maintenance therapy can be gradually reduced to once every 4 to 6 weeks to maintain remission. CR has been reported in up to 71.4% of patients with early stage MF, including long-term remissions of ≥ 10 years.³⁹⁻⁴⁶

PUVA is less effective in tumor stage/erythrodermic and folliculotropic MF; however, a combination with low-dose systemic agents (eg, interferon-alfa [IFNα]) may be considered.⁴⁷⁻⁴⁹ Common PUVA side effects include erythema, photodermatitis, pruritus, and nausea, managed with dose reduction/interruption.³⁹⁻⁴⁶

Ultraviolet B light (UVB) suppresses neoplastic T cell function and proliferation through antigen-presenting cell inhibition and increased keratinocyte cytokine production.⁵⁰⁻⁵² Narrowband UVB (NBUVB; 311 nm) is used more frequently than PUVA in early stage MF because of its similar efficacy;

Table III. Summary of treatments for patients with mycosis fungoides and Sézary syndrome

Therapy type	Treatment
Early stage MF (stage IA-IIA)	Steroids
Topical/skin-directed therapy	Phototherapy Nitrogen mustard Bexarotene Local radiation TSEBT
Refractory early stage MF (stage IA-IIA)	Combination therapy
	PUVA or NBUVB and IFNα (low-dose) PUVA or NBUVB and bexarotene (low-dose)
Advanced MF/SS (stage IIB-IVB)	
Skin-directed therapy	TSEBT
Immunomodulators	Interferons (IFNα and IFNγ) Retinoid/rexinoid (bexarotene) ECP
Biologic/targeted therapies	Alemtuzumab HDACis (eg, romidepsin and vorinostat) Antifolates (eg, methotrexate and pralatrexate)
Combined therapy	IFNα and phototherapy IFNα and retinoids/rexinoids Retinoid and phototherapy ECP and IFNα ECP and retinoids/rexinoids
Systemic chemotherapy	
Single-agent	Pegylated doxorubicin Purine/pyrimidine analogues (eg, gemcitabine)
Multiagent	CHOP and CHOP-like
Stem cell transplant	Autologous Allogeneic Nonmyeloablative allogeneic

Continued

there are also increased rates of skin cancer with PUVA. In stage IA/IB MF and parapsoriasis, CRR ranged from 54.2% to 91%,⁵³⁻⁶² with a higher efficacy in patch compared to plaque disease.⁵³ NBUVB is

Table III. Cont'd

Therapy type	Treatment
Investigational therapy	
	Lenalidomide
	Bortezomib
	CCR4 antibody
	TLR agonists
	Interleukins
	Anti-PD-1 agents
	Protein kinase C inhibitors
	Phosphoinositide 3-kinase inhibitors brentuximab vedotin

CHOP, Cyclophosphamide, doxorubicin, vincristine, and prednisone; *ECP*, extracorporeal photopheresis; *HDACi*, histone deacetylase inhibitors; *IFN α* , interferon- α ; *IFN γ* , interferon-gamma; *MF*, mycosis fungoïdes; *NBUVB*, narrowband ultraviolet B light phototherapy; *PD-1*, Programmed-Death-1; *PUVA*, psoralen plus ultraviolet A light phototherapy; *SS*, Sézary syndrome; *TLR*, Toll-like receptor; *TSEBT*, total skin electron beam therapy.

especially useful in hypopigmented MF.⁶³ UVB is generally well tolerated, with acute side effects of pruritus, burning, and erythema resolving with or without dose reductions. Photoaging and photocarcinogenesis are long-term risks of NBUVB, although less than with PUVA.⁶⁴⁻⁶⁶ Low-dose bexarotene (75-150 mg) may be combined with lower cumulative NBUVB to achieve a CR.⁶⁷

Radiation

Total skin electron beam therapy (TSEBT) involves the administration of ionizing radiation to the entire surface of the skin, with deeper penetration than both NM and phototherapy.^{68,69} With the advent of effective systemic therapies, TSEBT is reserved for rapidly progressive, refractory/relapsed, and extensive plaque (T2) or tumor (T3) disease. TSEBT decreases the burden of circulating malignant T cells that pass through the dermal vasculature and are highly radiosensitive; however, there are conflicting reports of its effectiveness in erythrodermic MF with blood involvement.⁷⁰⁻⁷²

Conventional TSEBT (30-36 Gy ionizing radiation over 8-10 weeks) may induce a CR,⁷²⁻⁷⁶ leading to 75% and 47% CRRs in T2 and T3 MF, respectively.⁷⁵ The duration of the response is limited (a median of 29 and 9 months for T2 and T3 disease, respectively, with a median follow-up time of 77 months).⁷⁵ Potential skin toxicity/necrosis limits repeat radiation courses. Subsequent skin-directed/systemic agents (eg, NM, PUVA, oral retinoids, IFN α , and extracorporeal photopheresis [ECP]) have shown mixed results.⁷⁶⁻⁸⁰ A second TSEBT course at a lower dose may be considered in select populations, depending upon the initial dose, tolerance, and the amount of time that has passed since the administration of the first course.⁷⁵

TSEBT toxicity is dose-dependent and includes erythema, xerosis, and desquamation, with long-term effects of alopecia, nail loss/dystrophy, xerosis, anhidrosis, and skin atrophy/necrosis.^{70,81,82} Low-dose radiation (10 Gy) may significantly decrease side effects and enable repeat radiation for disease control/palliation,⁸¹ although lower CRRs and response durations are seen with reduced doses (at 5-10 Gy, 16%; 10-20 Gy, 35%; 20-30 Gy, 34%; and >30 Gy, 62%).⁸¹

Local radiation therapy is effective for isolated/localized cutaneous tumors, or chronic, painful/ulcerated lesions, with a CRR of >90%.⁸³⁻⁸⁵ Multifractionated doses are standard, but single/few fractions of low-dose radiation may be sufficient: a single or 2 fractions of 7 to 8 Gy provides a CR in 95% of lesions.^{85,86} Lower responses are common in transformed MF and lower extremity lesions associated with poor circulation and wound healing. Radiosensitizing agents, such as histone deacetylase inhibitors, may work synergistically with low-dose local radiation therapy.^{87,88}

SYSTEMIC THERAPIES

Key points

- Single-agent systemic therapy (eg, bexarotene) is often used after skin-directed therapy is inadequate or in cases of advanced disease
- Immunomodulators, such as interferons and retinoids, are commonly used as first-line monotherapy in advanced mycosis fungoïdes and are also used in low-dose combination with topical agents
- Histone deacetylase inhibitors (vorinostat or romidepsin) are also effective single agents in skin, nodal, and blood disease
- Alemtuzumab is particularly active in erythrodermic mycosis fungoïdes/Sézary syndrome, with depletion of the central memory T-cell subset
- Chemotherapy is generally reserved for treatment refractory or rapidly progressive advanced mycosis fungoïdes
- Allogeneic stem cell transplantation, also reserved for advanced disease, may have curative potential in mycosis fungoïdes

Retinoids/bexarotene

Retinoids are immunomodulating agents that are structurally similar to vitamin A, with the first retinoids (eg, isotretinoin, acitretin, and etretinate) targeting RARs and leading to 44% to 67% ORRs in CTCL with variable response durations (range, 1-25

months).^{32,89-95} Oral bexarotene, which was been approved by the US Food and Drug Administration for refractory CTCL in all stages, has effects on cell differentiation and apoptosis and also downregulates CCR4 and E-selectin expression, affecting malignant T-cell trafficking to the skin.⁹⁶

In phase II and III trials of 94 patients with advanced stage MF (stages IIB-IVB) refractory to ≥ 2 standard therapies, ORRs of 45% and 55% were observed with daily doses of 300 or 650 mg/m², respectively.^{97,98} Decreased skin erythema/scaling and pruritus with temporary blood improvement was seen in erythrodermic MF and SS.^{99,100} The median response duration was 7 to 9 months.⁹⁷⁻¹⁰⁰ A daily dose regimen of 300 mg/m² was recommended based on the safety profile. Bexarotene has been safely combined at lower doses with IFN α , ECP, radiation, and phototherapy in treatment refractory or advanced disease^{67,101-106} but has not been shown to be better than bexarotene monotherapy.⁹⁹⁻¹⁰⁴

The most common side effects include hypertriglyceridemia, hypercholesterolemia, and central hypothyroidism, requiring dose adjustments, lipid-lowering, and thyroid medications.¹⁰¹ Other side effects include skin peeling, headache, arthralgias/myalgias, neutropenia/leukopenia, pancreatitis, and hepatitis.⁹⁷⁻¹⁰⁰

Interferons

IFNs have shown a wide range of biologic effects, and IFN α enhances T_H1 cell-mediated responses to malignant T-lymphocytes.^{107,108} IFN α is generally administered long-term, although the optimal dose and duration in MF/SS have not been established. Therapy should start at low doses (ie, 1-3 million units [MUs] 3 times weekly with gradual escalation [9-12 MUs daily as tolerated]).¹⁰⁸

IFN α monotherapy has shown efficacy in all stages, with 29% to 80% ORRs and 4% to 41% CRRs¹⁰⁷⁻¹¹⁰ (eg, 51 patients taking a mean daily low dose [2.7 MU] had 21 [41%] CRs, with 57% having disease-free survival of 7.5 months).¹¹¹ Greater efficacy is seen in earlier stages.¹¹¹ Maintenance IFN α therapy is continued for ≥ 3 months followed by slow tapering over 6 to 12 months if there is no recurrence.¹⁰⁸

Combination with retinoids does not appear to yield a higher response than IFN α alone^{104,107,108} and appears inferior to IFN α plus PUVA (38% CR with nonbexarotene retinoids vs 70% CR with IFN plus PUVA).¹¹² Combination with ECP results in decreased Sézary cell counts, although no studies have compared this to IFN α monotherapy.¹¹³⁻¹¹⁷ IFN-gamma may be effective in refractory MF/SS cases, even those refractory to IFN α .¹¹⁸

Neutralizing antibodies may decrease IFN efficacy, are dose-related,¹⁰⁷ and occur less frequently with combination therapies.⁴⁸ Most common side effects are also dose-related, including headaches, flu-like symptoms, fatigue, anorexia, weight loss, depression, peripheral neuropathy, and dysgeusia.¹⁰⁸

Extracorporeal photopheresis

ECP involves separating circulating mononuclear cells using a leukapheresis-based method, mixing with 8-methoxysoralen, exposure to ultraviolet A light (1-2 J/cm²), and reinfusion into the patient, with possible apoptosis induction of malignant T cells and the subsequent release of tumor antigens, leading to a systemic antitumor response.¹¹⁹ ECP was approved by the US Food and Drug Administration for the palliative treatment of CTCL in 1988 and is empirically given on 2 consecutive days every 2 to 4 weeks over >6 months.^{119,120}

ECP is primarily effective in erythrodermic CTCL, with 1 multicenter study of 37 patients showing a 73% ORR, including 24 patients with erythrodermic MF/SS.¹²¹ Later studies yielded a 35% to 71% ORR and a 14% to 26% CRR.¹²²⁻¹²⁶ Parameters associated with favorable response include short disease duration, clinical improvement in <6 months, normal CD8 $^+$ T cell count and CD4:CD8 ratio, low percentage of Sézary cells, and the absence of extracutaneous disease.¹²²⁻¹²⁷ Bexarotene or IFN α may be added for synergy.^{126,128-131} ECP may also be beneficial in a subset of limited disease (stage T1/T2) with abnormal flow cytometry (stage B1/B2).¹³² The few adverse events of ECP include catheter-related infection, hypotension caused by volume shifts, headache, fever, chills, and nausea secondary to 8-methoxysoralen.¹³¹

Targeted therapies

Alemtuzumab. Alemtuzumab is a humanized monoclonal antibody against the CD52 surface antigen on immune cells, including T/B cells, resulting in their depletion from the blood via neutrophil-mediated, antibody dependent cellular cytotoxicity and complement activation.¹³³⁻¹³⁵ CD52 expression is greater on CD4 $^+$ than CD8 $^+$ T cells.¹³⁶ Alemtuzumab was initially approved by the US Food and Drug Administration for the treatment of chronic lymphocytic leukemia, but is often effective in erythrodermic MF/SS, with ORRs of 86% to 100% (because of its depletion of central memory T cells that predominate in SS^{133,137-143}). Original studies recommended subcutaneous/intravenous doses of 30 mg 3 times weekly, but lower doses (10 mg 3 times/week) may be equally efficacious.¹⁴⁴

Alemtuzumab is associated with infusion reactions and prolonged immunosuppression, with earlier studies reporting opportunistic infections (eg, cytomegalovirus reactivation). Recent infectious prophylaxis has likely decreased this risk.¹⁴¹⁻¹⁴³

Histone deacetylase inhibitors

Histone deacetylase inhibitors (HDACis) may restore the expression of tumor suppressor and/or cell cycle regulatory genes by increasing histone acetylation with resultant growth inhibition and apoptosis. Vorinostat—approved by the US Food and Drug Administration for CTCL that has progressed beyond stage IB that is also refractory to 2 systemic therapies—is an oral HDAC class I and II inhibitor that also inactivates STAT3, which is constitutively expressed in CTCL, and enhances retinoid effects of RAR/RXR activation and gene transcription in vitro.^{145,146} A phase II trial showed a partial response in 22 of 74 patients (29.7%) with only 1 CR.¹⁴⁷ All patients received 400 mg of vorinostat once daily, with reductions to 300 mg daily for toxicity. Another phase II trial of 33 heavily pretreated CTCL patients found that sustained 400-mg daily dosing is more effective and less toxic than intermittent dosing (twice-daily 300-mg regimens).¹⁴⁸ A similar ORR of 24.2% was noted.

Romidepsin, which is approved by the US Food and Drug Administration for advanced CTCL that is refractory to ≥ 1 systemic therapy, inhibits class I and II HDACs and is intravenously administered at a weekly dose of 14 mg/m^2 for 3 weeks, 1 week off, and continued until intolerance or disease progression. Two phase II trials have evaluated romidepsin in advanced-stage MF, with 1 showing a 36% response rate (26/68), including 5 patients with CR.^{149,150} Significant pruritus reduction was reported in patients; however, this did not correlate with clinical response.¹⁵¹

The most common side effects were gastrointestinal disturbances (ie, nausea and anorexia), fatigue, hematologic abnormalities (ie, thrombocytopenia, anemia, lymphopenia, and neutropenia), and infectious complications.^{149,150,152} Electrocardiography assessments showed T wave flattening in 71% of patients, less common ST depression, and rare QTc prolongations (2%).^{149,150} A new oral pan-deacetylase (class I-IV) inhibitor panobinostat, which has a longer half-life, is currently being studied.¹⁵³

Denileukin diftitox. The IL-2-alfa receptor or CD25 is a target for denileukin diftitox, a fusion toxin (IL-2 linked with diphtheria toxin) that was approved by the US Food and Drug Administration in 1999 for recurrent/persistent CTCL with $\geq 20\%$ expression of CD25 on malignant T cells, but it is currently unavailable by manufacturer.¹⁵⁴ After interleukin-2 receptor

binding, denileukin diftitox is internalized, inducing apoptosis by blocking protein synthesis.^{155,156} Phase III studies found RRs of 23% and 38% at low dose (9 mg/kg/day) and 36% and 49% at 18 mg/kg/day, respectively (median duration, 7 months).¹⁵⁷⁻¹⁵⁹ Response may be seen in patients with $<20\%$ CD25 expression.¹⁶⁰ Adverse effects include acute infusion-related events (eg, fever, rash, chills, dyspnea, or hypotension), myalgias, elevated serum transaminase levels, and vascular leak syndrome.^{157,159}

CHEMOTHERAPY

Antifolates

The reduced folate carrier type 1, an oncofetoprotein that is predominantly expressed in the membranes of fetal and tumor cells, mediates the cellular uptake of folates and antifolate drugs, including methotrexate and a newer agent, pralatrexate (which is approved by the US Food and Drug Administration for relapsed/refractory peripheral T-cell lymphoma).^{161,162} Both antifolates are substrates for folylpolyglutamate synthetase and potently inhibit dihydrofolate reductase.¹⁶³

Low-dose methotrexate (median weekly dose, 25 mg) has an ORR of 33% and 58% in plaque (T2) MF and erythrodermic MF, respectively, with an increased ORR (82%) at higher doses ($60-240 \text{ mg/m}^2$ intravenously).¹⁶⁴⁻¹⁶⁶ In a study on relapsed/refractory CTCL, an optimal intravenous dose of pralatrexate of 15 mg/m^2 weekly for 3 to 4 weeks was identified with an ORR of 45%, including patients previously treated with methotrexate.¹⁶⁷ Common side effects include gastrointestinal (eg, nausea/vomiting, mucositis, and ulcers), hematologic (eg, leukopenia, anemia, and thrombocytopenia), and hepatic toxicities.^{167,168}

Single and multiagent chemotherapy. Both single and multiagent chemotherapy have been used in refractory/relapsed CTCL. Gemcitabine and pegylated liposomal doxorubicin are relatively new effective monotherapies with ORRs of 68% and 75% for gemcitabine^{169,170} and 40.8% and 88% for doxorubicin.^{171,172} Multiagent chemotherapy regimens including cyclophosphamide, doxorubicine, vincristine, and prednisone-based regimens have shown comparable efficacy, but with greater toxicity.¹

Hematopoietic stem cell transplantation. Hematopoietic stem cell transplantation—specifically allogeneic stem cell transplantation—may have a curative potential in advanced MF/SS, although no large series exist and conditioning regimens are largely driven by institutional preference.¹⁷³⁻¹⁷⁵ Despite reported CRRs in most patients treated by autologous stem cell transplantation, relapses are frequent, occurring within 6 months posttransplant.¹⁷⁶⁻¹⁸⁰ Allogeneic transplants achieve

more durable CRRs, which are largely attributed to the donor T/natural killer (NK) cell–mediated graft versus lymphoma effect. Donor lymphocyte infusions in the early posttransplant period or in relapsed disease may enhance this effect.^{181,182} Response durations of 6 years posttransplant have been reported.^{183,184} Treatment-related mortality (ie, life-threatening infections and graft versus host disease) occurs in approximately 30% of cases. Reduced-intensity nonmyeloablative (mini) allogeneic stem cell transplantation potentially offers a graft versus lymphoma effect with decreased conditioning regimen–related toxicity.^{183,185–187}

Other investigational therapies

Lenalidomide, a thalidomide analog that has been approved by the US Food and Drug Administration for the treatment of myelodysplastic syndrome and relapsed/refractory multiple myeloma and mantle cell lymphoma, increases T_H1-cytokine production and enhances T and NK cell–mediated killing.¹⁸⁸ A phase II trial of 32 patients with advanced/refractory CTCL showed an ORR of 29%.¹⁸⁹ Side effects include temporary flares of skin disease and circulating Sézary cells, cytopenias, and fatigue/malaise.

Toll-like receptor agonists, which mimic bacterial antigens and stimulate the innate immune response, have been used in CTCL patients,^{190,191} as have interleukins-12 and -2.^{192–195} In 2 phase II studies of zanolimumab, a monoclonal antibody with specificity for CD4 receptors on T cells, a 56% ORR at 560 to 980 mg was observed, with early (8-week) durable response, and side effects similar to other T cell–targeted therapies.¹⁹⁶ T-cell receptor CCR4, which is involved in the skin-homing of malignant T cells, is another potential therapeutic target in CTCL.^{197–201}

Proteasomes function in nonlysosomal degradation of intracellular proteins, regulating cell survival; bortezomib, a proteasome inhibitor, which also downregulates the transcription factor nuclear factor- κ B, has shown efficacy in relapsed/refractory CTCL (67% ORR) with side effects of myelosuppression and sensory neuropathy.^{202,203} Other targeted therapies currently in clinical trials include antibody-drug conjugate directed to CD30 surface protein (brentuximab vedotin), anti–PD-1 therapies, phosphoinositide 3-kinase inhibitors, and protein kinase C inhibitors.^{204–209}

GENERAL HEALTH CARE

Key points

- Important quality of life considerations include pruritus, xerosis, and the prevention of skin infections

- Treatment-related toxicities may require dose adjustments, particularly in the elderly, patients with advanced disease, and patients with multiple comorbidities

Many patients are disabled by their pruritus and skin appearance. Emollients should be used for dryness and scaling, and the application of midpotency steroids, particularly triamcinolone 0.1% ointment once or twice daily, is especially useful in SS. A short-term course with systemic steroids often gives immediate symptomatic relief. Oral antihistamines, gabapentin, aprepitant, and/or mirtazapine may be of benefit for pruritus. Patients with more widespread cutaneous disease or generalized erythroderma need screening for secondary infections (eg, staphylococcus, streptococcus, dermatophytes, and herpesviruses) and appropriate systemic treatment. Bleach baths, as given in children with severe atopic dermatitis, can minimize colonization of *Staphylococcus aureus*.²¹⁰ Patients with advanced disease are particularly at increased risk for infections and sepsis given their immunosuppressed state.

In summary, while there is no cure for MF and SS, treatment is directed at clearing cutaneous and extracutaneous disease, minimizing disease recurrence, and preventing disease progression. Treatment-associated toxicities can be problematic, particularly in elderly patients. Dose adjustments are often required in those patients, because treatment is palliative and must be balanced against the increased risk for toxicities.

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Safety of dermatologic medications in pregnancy and lactation

Part I. Pregnancy

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After completing this learning activity, participants should be able to prescribe select dermatologic medications during pregnancy; to educate reproductive-age women, as well as expectant mothers, regarding the benefits and potential risks of taking select dermatologic medications during pregnancy; and to appropriately monitor for side effects in the expectant mother and newborn when administering select dermatologic medications during pregnancy.

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Dermatologists are frequently faced with questions about the safety of commonly prescribed topical and systemic medications during pregnancy and lactation from women of childbearing age who are pregnant, considering pregnancy, or breastfeeding. Safety data, particularly regarding medications that are unique to dermatology, can be difficult to locate and are not consolidated in a single reference guide for clinicians. Parts I and II of this continuing medical education article provide a capsule summary of key points for the most commonly prescribed dermatologic medications to facilitate patient medication risk counseling in pregnancy. A summary table details safety classification data for 3 primary international classification systems: the US Food and Drug Administration, the Swedish Catalogue of Approved Drugs, and the Australian Drug Evaluation Committee. In addition, this table includes an alternative pregnancy classification system developed by a consortium of active members of teratology societies in the US and Europe detailed in *Drugs during Pregnancy and Lactation: Treatment Options and Risk Assessment* and a safety classification system developed for breastfeeding mothers detailed in *Medications and Mother's Milk*. (J Am Acad Dermatol 2014;70:401.e1-14.)

Key words: acne; antibiotic; antifungal; antihistamines; antiviral; atopic dermatitis; biologics; breastfeeding; breast milk; corticosteroid; cosmetics; fetus; gestation; lactation; medication safety; nursing; phototherapy; pregnancy; psoriasis; surgery; trimester.

This month's Continuing Medical Education articles consolidate safety data for patients who are pregnant (Part I) and breastfeeding (Part II) while undergoing dermatologic therapy. Key safety data for commonly prescribed dermatologic medications in pregnancy are described below and summarized in Fig 1. Details regarding the safety classification data for 3 primary international classification systems are provided in Table I.

TOPICAL ANTIINFLAMMATORY DRUGS IN PREGNANCY

Corticosteroids

Multiple large, population-based studies and a Cochrane review have not shown an increased risk of malformations, including oral cleft palate, or

Abbreviations used:

ADEC:	Australian Drug Evaluation Committee
BBUVB:	broadband ultraviolet B light
FDA:	Food and Drug Administration
HCQ:	hydroxychloroquine
IVIG:	intravenous immunoglobulin
MMF:	mycophenolate mofetil
NBUVB:	narrowband ultraviolet B light
NTD:	neural tube defect
PUVA:	psoralen plus ultraviolet A light phototherapy
TNF:	tumor necrosis factor

preterm delivery with topical corticosteroids.¹⁻⁷ Fetal growth restriction has been reported with use of potent topical corticosteroids during the third

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trimester, particularly when using >300 g.^{2,4,8} Topical corticosteroids will also increase the risk of developing stretch marks. Evidence-based guidelines recommend mild to moderate cortisones over potent corticosteroids, which should be used in short durations.⁹

Calcineurin inhibitors

Oral tacrolimus is associated with prematurity and low birth weight, and has a safety profile similar to that of cyclosporine. When used topically, calcineurin inhibitors are poorly absorbed systemically because their molecular size prevents penetration. Because there are no studies on safety in human pregnancies, when no alternatives exist, topical use on small surfaces is permissible.¹⁰

Coal tar

While animal studies show that maternal exposure to high-dose coal products resulted in perinatal mortality, and increased risk of cleft palates, and small lungs in offspring, the literature on human exposure has failed to reveal any developmental effects.^{11,12} Although there are no indications of teratogenic effects in humans, coal tar should ideally not be used in pregnancy, but incidental use does not require any action.¹⁰

Calcipotriene

In animal studies, calcipotriene, a vitamin D analog, resulted in an increased incidence of skeletal abnormalities, including incomplete ossification of pubic bones and forelimb phalanges.¹³ Generally, D-hypervitaminosis should be avoided in pregnancy, but use in the recommended dosage range (≤ 100 g/wk of a 0.005% solution) does not lead to a disturbance in calcium homeostasis.¹⁰ Because there are no studies on safety in human pregnancies, when no alternatives exist, topical use on small surfaces is permissible.

SYSTEMIC THERAPY FOR PSORIASIS

Methotrexate

Methotrexate has a well documented history as a teratogen and is absolutely contraindicated during pregnancy, although not all outcomes are poor in those with inadvertent exposure.¹⁴ Methotrexate is associated with miscarriage and numerous congenital malformations, such as developmental delay and craniofacial, limb, cardiopulmonary, and gastrointestinal abnormalities.¹⁵

Cyclosporine

The majority of data on cyclosporine comes from transplant recipients, who are generally given higher

doses (8-10 mg/kg/day) than dermatologic patients. Cyclosporine is not an animal or human teratogen in >1000 pregnancies, but risk of low birth weight and prematurity has been shown in cases of complicated health status.¹⁶⁻²⁰ Cohorts have been followed through early childhood, with no detectable long-term neurodevelopmental, nephrotoxic, or immunologic effects in the children.²¹⁻²³ Cyclosporine can cause maternal hypertension and should be reserved as a rescue therapy for severe disease.

Biologics

Limited data for tumor necrosis factor- α (TNF α) inhibitors, including infliximab, etanercept, and adalimumab, indicate numerous cases of safe use during pregnancy and no clear pattern of malformations. One group noted an association between the use of etanercept and the development of vertebral anomalies, anal atresia, cardiac anomalies, tracheoesophageal fistula, esophageal atresia, renal abnormalities, and limb anomalies (VATER syndrome), biologically plausible based on results seen in animal models.²⁴ A follow-up review submitted to the US Food and Drug Administration (FDA) revealed higher rates of VATER if combination etanercept and infliximab were used.²⁵ Responses to this study challenge the authors' definition of what constitutes VATER, ultimately declaring the data uninterpretable.²⁶ They remain pregnancy US FDA pregnancy class B.

There is an increased rate of spontaneous abortion if etanercept is used during the first trimester.²⁷ In the third trimester, immunoglobulin G readily crosses the placenta, and there are detectable levels in infant serum of infliximab from 2 to 7 months after birth.²⁸ Live vaccines need to be avoided in infants with in utero exposure at least the first 6 months of life because they may be unable to mount an immune response, as was the case in an infant who died of disseminated Bacillus-Calmette-Guérin after receiving his vaccination at 3 months of age.²⁹

Data are extremely limited for adalimumab and the interleukin-12/-23 inhibitor ustekinumab. There were no maternal, fetal, or infantile toxicities in animal studies, but there have been reports of spontaneous abortions with both.³⁰⁻³² TNF α inhibitors can be used with caution for severe, recalcitrant disease, but it remains uncertain whether routine use during pregnancy is advisable.³³

Acitretin

Retinoic acid is important in development of the brain, face, thymus, heart, and spinal cord during embryogenesis, and all systemic retinoids are

Continuing Medical Education JE Murase, M.D. MM Heller, M.D. DC Butler, B.S.											Level of Evidence			
Pregnancy: International Systems			Pregnancy: Evidence Based Medicine								Lactation: Hale			
FDA			Schaefer C, Peters PWJ, Miller RK. Drugs during pregnancy and lactation: treatment options and risk assessment. 2nd ed. Amsterdam; Boston: Elsevier Academic Press; 2007.								Hale TW. Medications and Mothers' Milk, 14 ed			
FASS			Categories: A, B, C, D, X								IA Meta-analysis of RCTs			
ADEC			Categories: A, B:1, B:2, B:3, C, D								IB ≥1 RCTs			
Time Intervals: Embryonic period (until week 12), Fetal period (from week 13) & Peripartum (last month of gestation)			S Single dose and/or low dosages probably tolerable								IIA non-randomized controlled studies			
			T Potentially teratogenic or toxic								IIB any quasiexperimental study			
			X Contraindicated (No rational indication for use during pregnancy)								III comparative, correlational, case-control			
			L1 Drug of 1st choice (In general, well-tolerated during pregnancy)								IV expert reports/opinions or clinical reports			
			L2 Drug of second choice (Use only if better-tested options fail; there is often insufficient experience during pregnancy)								Lactation: Hale			
			L3 Safer								Hale TW. Medications and Mothers' Milk, 14 ed			
			L4 Moderately Safe								L1 Safest			
			L5 Possibly Hazardous								L2 Safer			
			L6 Contraindicated								L3 Moderately Safe			
			L7 Possibly Hazardous								L4 Contraindicated			
			L8 Contraindicated								L5 Contraindicated			
DERMATOLOGIC MEDICATIONS			PREGNANCY								LACTATION			
			International Systems			Evidence Based Medicine			Recommendations (Level of Evidence)			Hale		
			FDA	FASS	ADEC	Embryo	Fetal	Peri				Recommendations (Level of Evidence)		
Topical anti-inflammatory	Topical Corticosteroids			C	C	A, B3, C	1	1	1	Prefer mild-mod potency(IV) ⁴			L1-3 Ok apply nipple, except Class I(IV)	
	Pimecrolimus			C	B:2	B3	Min data: avoid			Avoid (IV) ¹⁰			L2 Contraindicated on nipple, since oral absorption may be high(IV)	
	Tacrolimus			C	B:3	C	Min data: avoid			Avoid (IV) ¹⁰			L4nipple Contraindicated on nipple, since oral absorption may be high(IV)	
	Coal Tar			—	—	—	Min data: avoid			Avoid; mutagenic/carcinogenic(III) ¹²			— Avoid or use minimally(IV)	
	Calcipotriene			C	C	B1	≤100g/wk of 0.05% solution has no effect on calcium homeostasis			Use small surfaces permissible(IV) ¹⁰			L3 Compatible; limit to <20% surface area (IV)	
Systemic therapy for psoriasis	Oxsoralen (PUVA)			C	—	B2	—	—	—	Avoid; mutagenic/carcinogenic(III) ³⁹			— Pump & discard for ≥1 day(IV)	
	Methotrexate			X	D	D	X	X	X	Contraindicated(III) ¹⁴			L5 Pump & discard for ≥4 days(IV)	
	Cyclosporine *(888)522-5581			C	C	C	Risk of fetal growth restriction/prematurity/maternal HTN			Avoid; no long-term ill effects in child cohorts(III) ¹⁸			L3 No adverse effects reported(IV)	
	Etanercept *(877)311-8972			B	B:2	B2	X	X	X	Uncertain if advisable(III) ²⁴			L3 No adverse effects reported(IV)	
	Adalimumab *(877)311-8972			B	C	C	X	X	X	Uncertain if advisable(IV) ³¹			L2 No adverse effects reported(IV)	
Other systemic anti-inflammatory	Infliximab *(800)526-7736			B	C	C	X	X	X	Uncertain if advisable(III) ²⁴			L3 No adverse effects reported(IV)	
	Ustekinumab *(800)526-7736			B	B:1	—	X	X	X	Uncertain if advisable(IV) ³³			L2 Min data: avoid(IV)	
	Corticosteroids			C	C	A	2	2	2	↑risk of oral clefts in 1st tri(IV) ¹⁵			L2 Use <3wks;nurse after ≥24hrs(IIa) ¹³⁹	
	Hydroxychloroquine			C	B:3	D	1	1	1	1st line active lupus(IV) ⁴⁵			L2 Uncertain if advisable(IV)	
	Dapsone			C	—	B2	Reserve for specific indications			Associated with hyperbilirubinemia/hemolytic anemia(IV) ^{54,55}			L4 Case of hemolytic anemia, avoid in G6PD/hyperbilirubinemia(IV)	
Systemic anti-pruritics	Mycophenolate mofetil *(800)617-8191			D	D	D	X	X	X	Contraindicated; can interfere with hormonal contraception(IV) ⁵⁹			L4 Avoid, likely enters milk(IV)	
	Azathioprine			D	D	D	2	2	2	Reduce dose if preg woman is leukopenic in 3rd tri; can interfere with IUD efficacy (III) ⁶¹			L3 Infant TPMT levels; monitor for decreased growth/immunosuppression(IV)	
	IVIG			C	—	—	Reserve for specific indications			Used for infertility tx, crosses the placenta ≥32 wks gestation(IV) ⁵⁴			L2 Can be used safely(III) ¹³⁶	
	Rituximab*(888)835-2555			C	—	—	Impacts fetal B-cell development			Avoid, neonatal hematologic abnormalities(III) ⁶⁸			L2 Min data: avoid(IV)	
	Chlorpheniramine **(1st gen)			B	—	A	Preferred over 2nd gen			Preferred above 2nd gen (III) ⁴¹			L3 Observe for sedation(III) ³⁵	
Acne, Cosmetics & Surgery	Diphenhydramine **(1st gen)			B	B:2	A	1	1	T	↑uterine contractions, especially IV or overdose in 3rd tri(III) ⁷¹			L2 Observe for sedation(III) ³⁵	
	Hydroxyzine **(1st gen)			C	C	A	Monitor for infant withdrawal symptoms w/ regular maternal use			May be associated with an ↑risk of congenital malformations(III) ⁴¹			L1 Observe for sedation, tachycardia, dry mouth(III) ³⁵	
	Cetirizine **(2nd gen)			B	B:1	B2	2	2	2	2nd line after loratadine (III) ⁷¹			L2 Observe for sedation(III) ³⁵	
	Fexofenadine **(2nd gen)			C	B:2	B2	Min data			Use alternatives(IV) ⁷¹			L2 Observe for sedation(III) ³⁵	
	Loratadine **(2nd gen)			B	B:3	B1	1	1	1	1st line 2nd gen antihistamines(III) ⁷¹			L1 Observe for sedation, tachycardia, dry mouth(III) ³⁵	
Acne, Cosmetics & Surgery	Doxepin			Biopical Coral	—	C	1	1	T	Hypotonia, emesis, and weak suck in newborns with 3rd tri exposure (III) ⁷¹			L5 Sedation, respiratory depression, hypotonia, emesis(IV)	
	Lidocaine			B	—	A	1	1	1	Safe as local anesthetic(III) ⁸⁰			L2 Safe as local anesthetic(IV)	
	Epinephrine			C	—	A	Local anesthetic use is acceptable in pregnancy			Safe as local anesthetic(III) ⁸⁰			L1 Safe as local anesthetic(IV)	
	Minoxidil (topical)			C	B:3	C	Oral: infant hypertrichosis, disappears over first 3 months			Avoid, cases of newborns with birth defects(IV) ⁸²			L2 Compatible; low systemic effect when used topically(IV)	
	Botulinum toxin A			C	B:3	B3	Avoid cosmetic products			Fetal movement observed in mother paralyzed w/ systemic botulism(III) ⁹⁶			L3 Prob compatible; case of nursing mother w/ botulism and no fetal adverse effects(IV)	
Hydroquinone			C	—	—	—	—	—	Avoid; mutagen(IV) ¹⁰			L3 Prob compatible(IV)		
Tretinoin (topical)			C	B:3	D	T	T	T	Large studies indicate safe, but most experts do not recommend(IIb) ⁹⁸			L3 Unlikely absorbed in significant quantities, likely safe(IV)		
Spironolactone			D	B:3	B3	2	2	2	Avoid, male feminization(III) ⁴¹			L2 Possible suppression of milk(IV)		
Tazarotene			X	—	—	X	X	X	Teratogen(IV) ¹⁰⁰			L3 Limit to <20% surface area(IV)		

*Enroll if pregnancy occurs while on these medications or within 8 wks of treatment

**If 1st gen antihistamines are too sedating, 2nd gen antihistamines can then be considered. Antihistamines may be associated with ↑risk of retrolental fibroplasia in premature infants with use within 2 wks of delivery.

Fig 1. Pregnancy: evidence-based medicine.

Topical antibiotics	Benzoyl peroxide	C	A	—	May be used on limited areas			Metabolized to benzoic acid, food derivative(IV) ¹⁰¹	—	Compatible(IV)
	Clindamycin	B	B:1-2	A	Min data: no known fetal effects			Case of pseudomembrane colitis w/ intravaginal use	L2	Compatible(IV)
	Erythromycin	B	—	A	Min data: no known fetal effects			Presumed safe	—	Compatible(IV)
	Azelaic acid	B	B:1	B1	Min data: no known fetal effects			Skin absorption is about 4-8%	L3	Normal constituent of milk; found in wheat, rye, and barley(IV)
	Sulfacetamide	C	—	—	Min data: no known fetal effects			Skin absorption is about 4%	—	Compatible(IV)
	Metronidazole	B	B:1	B2	Min data: no known fetal effects			Presumed safe	L3	Compatible(IV)
	Mupirocin	B	B:1	B1	Min data: no known fetal effects			Local use ok; limited sys absorption	L1	Topical antibiotic of choice(IV)
	Bacitracin	C	—	—	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Min data: compatible(IV)
	Polymyxin B	B	—	—	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Compatible; use in small amounts if applied to nipple(IV)
	Neomycin	C	—	D	Min data: no known fetal effects			Local use ok; limited sys absorption	L2	Min data: compatible(IV)
Systemic antibiotics	Penicillins	B	A	A, B1-3	1	1	1	Antibiotics of choice(IIb) ¹¹	L1	Compatible(III) ¹³⁹
	Cephalosporins	B	A	A, B1-2	1	1	1	Safe, older cephalosporins preferred(IIb) ⁴¹	L1-2	Compatible(III) ¹³⁹
	Erythromycin (not erythromycin estolate!)	B	D	A	2	1	1	↑risk of heart defects/pyloric stenosis; estolates cause maternal hepatotoxicity in 2nd tri(IIa) ¹⁰⁸	L2, L3 early	Compatible; may cause pyloric stenosis with early postpartum use(III) ¹³⁸
	Azithromycin	B	B:1	B1	Min data: 2nd choice macrolide			2nd line after erythro(III) ¹⁰⁸	L2	Min data: prob compatible(III) ¹³⁸
	Clarithromycin	C	B:3	B3	2	2	2	2nd line after erythro(III) ¹⁰⁸	L2	Min data: prob compatible(III) ¹³⁸
	Clindamycin	B	B:1-2	A	Only if penicillins, macrolides and cephalosporins are ineffective			2nd line b/c of pseudomembranous colitis(IV) ¹⁰⁹	L2	Compatible; case of child w/ transient bloody stool episode(IV)
	Rifampin	C	C	C	1	1	1	Tx of choice for tuberculosis; give vit K prophylaxis peripartum(IV) ¹¹⁰	L2	Compatible(IV)
	Sulfonamides	B, C	C	C	2	2	X	↑ risk of heart defects, preterm birth, hyperbilirubinemia peripartum(III) ¹¹²	L3	Avoid in G6PD/hyperbilirubinemia(IV)
	Trimethoprim	C	B:3, C	C	2	2	2	May cause folate depletion(III) ^{112,114}	L2	Supplement with folic acid(IV)
	Quinolones (Ciprofloxacin/Oflloxacin/ Norfloxacin)	C	B:3	B:3	2	2	2	Use only in complicated cases of antibiotic resistant infection(IV) ¹⁰	L3	Observe for diarrhea; case of pseudomembrane colitis(IV)
Topical anti-fungals	Tetracyclines	D	D	D	2	X	X	Contraindicated if >15wks b/c ↓ bone growth/teeth discoloration(III) ¹⁰	L2-4	May cause ↓ bone growth with prolonged exposure (>3wks)(IV)
	Nystatin	Topical, Avaginal	A	A	1	1	1	Topical anti-fungal of choice(IV) ¹⁰	L1	Best studied: 1st therapy(IV)
	Clotrimazole	B	A	A	2	1	1	Topical anti-fungal of choice(IV) ¹⁰	L1	Best studied: 1st therapy(IV)
	Terbinafine	B	B:1	B1	Min data: no known increased risk			Animal data suggests low risk(IV) ¹⁰	L2	Min systemic absorption(IV)
	Ciclopirox	B	A	—	Min data: no known increased risk			Probably compatible(IV) ¹⁰	L3	Min systemic absorption(IV)
Systemic anti-fungals	Selenium sulfide	C	A, B:3	—	Local application is acceptable			Local application for limited time(IV) ¹⁰	L3	Safe, case of lactation suppression(IV)
	Griseofulvin	C	—	B3	2	2	2	Avoid, case of conjoined twins(IV) ¹¹⁸	L2	Min data: avoid(IV)
	Fluconazole	C	B:3	D	2	2	2	Human data suggest risk(III) ¹¹⁹	L2	Best studied, compatible, safe in preterm infants(IV)
	Ketoconazole	C	B:3	B3	2	2	2	Human data suggests risk(IV) ¹⁰	L2	Min data: probably compatible(IV)
	Itraconazole	C	B:3	B3	2	2	2	Human data suggests risk(IV) ¹⁰	L2	Can concentrate in milk(IV)
Systemic anti-virals	Terbinafine	B	B:1	B1	Min data: avoid			Postpone tx of onychomycosis(IV) ¹⁰	L2	Avoid prolonged use(IV)
	Acyclovir	B	B:3	B3	1	1	1	1st line for herpes; prophylaxis begins at 36 wks gestation(IIb) ¹²⁷	L2	Compatible(IV)
	Famciclovir	B	B:2	B1	Min data			3rd line(IV) ¹⁰	L2	3rd line(IV)
	Valacyclovir	B	B:3	B3	More data than famciclovir			2nd line(IV) ¹⁰	L1	2nd line(IV)
Topical anti-virals: Warts	Trichloroacetic acid	—	—	—	Possible tx for condylomata acuminata			2nd line after destructive therapy(IV) ¹⁰	—	Min data: prob compatible(IV)
	Squaric acid	—	—	—	—	—	—	Min data in animals/humans	—	Min data: prob compatible(IV)
	Salicyclic acid	C	C	—	Use on limited areas for limited time is acceptable			Local application for limited time(IV) ¹⁰	L3	Compatible for local, topical use(IV)
	Podophyllin	X	—	—	Absolutely contraindicated			Maternal/fetal death; heart/ear/extremity defects; psych sxss(IV) ¹⁰	L3	Uncertain if advisable(IV)
	Podofilox	C	B:1, C	—	—	—	—	Min data in animals/humans	L3	Uncertain if advisable(IV)
	Cantharidin	C	—	—	—	—	—	Min data in animals/humans	—	Uncertain if advisable(IV)
	Imiquimod	C	B:1	B1	—	—	—	[Min data, no teratogenicity(III)] ^{7#}	—	Min data: prob compatible(IV)
Scabies & Lice	Lindane	C	—	B3	T	T	T	Avoid; teratogen(IV) ¹⁰	L4	Avoid; may cause ↑LFTs, seizures & hypersensitivity(IV)
	Benzyl benzoate (Banned in US)	C	B:2	B2	1	1	1	Used in Europe(IV) ¹⁰	—	Prob compatible(IV)
	Permethrin	B	B:1	B2	2% absorbed with topical use			1st line for scabies; 2nd line for lice (1st line occlusive tx)(III) ¹⁰	L2	1st for scabies: apply head to toe (infants) & neck down (adults)(IV)
	Pyrethrins	C	—	B2	1	1	1	2nd line for lice (1st line occlusive tx)(IV) ¹⁰	L2	2nd line for lice (1st line occlusive tx)(IV)
	Crotamiton	C	—	B2	<1% is absorbed with topical use			Min data: likely safe	—	Min data: likely safe(IV)
	Malathion	B	B:1	B2	—	—	—	Pesticide, avoid if possible	L4	Min data: avoid; may cause respiratory depression(IV)
	Precipitated sulfur	C	—	—	—	—	—	Min data: likely safe	—	Min data: likely safe(IV)
	Ivermectin	C	—	B3	Only use for compelling indication			Min data: systemic tx for scabies if resistant to topical tx(IV) ⁴¹	L3	If topical permethrin fails, ivermectin can be used(IV)

Disclaimer: This material is intended to serve as an initial reference, *not* as a complete resource. It does not include information concerning every therapeutic agent, laboratory, or diagnostic test or procedure available. It is intended for physicians and other competent healthcare professionals who will rely on their own discretion and judgment in medical diagnosis and treatment.

Fig 1. Continued.

Table I. Definition of the pregnancy risk categories used by the United States Food and Drug Administration, the Swedish Catalogue of Approved Drugs, and the Australian Drug Evaluation Committee

Comparison of drug risk classification systems*		
US FDA	FASS	ADEC
A—Clinical data show no evidence of risk to the fetus (4%)	A—Reliable clinical data indicate no evidence of disturbance of the reproductive process (22%)	A—Extensive clinical experience in pregnant women and women of childbearing age has shown no increase in the frequency of malformations or other harmful effects on the fetus (27%)
B—Clinical data are limited or not available, but animal studies show no evidence of risk to the fetus, or clinical data show no evidence of risk to the fetus, but animal studies show adverse effects to the fetus (23%)	B—Clinical experience of use in pregnant women is limited or insufficient. Classification is based on animal data, by allocation to 3 subgroups (B:1, B:2, and B:3) <ul style="list-style-type: none"> B:1—Animal experiments have not given evidence of an increased incidence of fetal damage; similar to FDA category B (11%) B:2—Animal experiments are inadequate; similar to FDA category C (12%) B:3—Reproduction toxicity studies in animals have revealed an increased incidence of fetal damage, the significance of which is considered uncertain in humans; similar to FDA category C (12%) 	B—Human data are lacking or inadequate. Limited use in pregnant women and women of childbearing age has shown no increase in the frequency of malformation or other harmful effects on the human fetus. Classification is based on available animal data into 3 subcategories (B:1, B:2, and B:3). Note: allocation to category B does NOT imply greater safety than category C <ul style="list-style-type: none"> B:1—Studies in animals have not shown evidence of an increased occurrence of fetal damage; similar to FDA category B (8%) B:2—Studies in animals are inadequate or lacking, but available data show no evidence of an increased occurrence of fetal damage; similar to FDA category C (19%) B:3—Studies in animals have shown evidence of an increased occurrence of fetal damage, the significance of which is considered uncertain in humans; similar to FDA category C (11%)
C—Clinical data are not available and animal studies are not available, or clinical data are not available, but animal studies show adverse effects to the fetus (45%)	C—Data suggest pharmacologic effects may have adverse effects on the reproductive process (30%)	C—Drugs which, owing to their pharmacologic effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible (24%)
D—Positive evidence of risk to the fetus from clinical data (22%)	D—Data indicate an increased incidence of malformations in humans (13%)	D—Drugs which have caused, are suspected to have caused, or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacologic effects. Note: drugs in category D are not absolutely contraindicated in pregnancy. In some cases, the D category has been assigned on the basis of suspicion (10%)
X—Contraindicated based on animal studies or clinical data (6%)		X—Contraindicated in pregnancy (1%)

ADEC, Australian Drug Evaluation Committee; FASS, Farmaceutiska Specialiteter i Sverige (Swedish Catalogue of Approved Drugs); FDA, Food and Drug Administration.

*For each organization, the percentage of medications that fall within each pregnancy category is indicated in parentheses (according to Addis et al¹³³).

completely contraindicated in pregnancy. Women of childbearing age should be discouraged from taking acitretin because it is necessary to avoid pregnancy for 3 years after discontinuing use.

PHOTOTHERAPY

Narrow- and broadband ultraviolet B light phototherapy

Both narrowband (NBUVB) and broadband (BBUVB) ultraviolet B light phototherapy are considered safe options in pregnancy. Phototherapy may worsen melasma, so advise facial shielding depending on patient skin type. Folic acid levels have been shown to decrease with both NBUVB and BBUVB, and folate deficiency in the first trimester could predispose to the development of neural tube defects (NTDs).^{34,35} NTDs have been demonstrated in three patients with sunbed exposure in early pregnancy.³⁶ Core temperature readings in a small cohort suggested that phototherapy is unlikely to result in hyperthermia, but cooling measures and avoidance of high doses of heat is advisable. Measure folic acid levels in phototherapy patients considering pregnancy, and initiate appropriate folic acid supplementation during phototherapy.^{36,37}

Psoralen plus ultraviolet A light phototherapy

Psoralen plus ultraviolet A light phototherapy has not been shown to increase risk of congenital malformations or infant mortality, but there was a marked increase in low birth weight babies.^{38,39} Because psoralen is a known mutagen and teratogen, it is recommended to avoid psoralen plus ultraviolet A light phototherapy treatment during pregnancy.

OTHER SYSTEMIC ANTIINFLAMMATORY DRUGS

Systemic corticosteroids

Prednisone, a nonfluorinated corticosteroid, is the preferred choice because placental enzymes limit passage to the embryo.⁴⁰ Studies note a 3-fold increased risk of orofacial clefts 4 weeks before conception to 12 weeks after conception; lip formation occurs during weeks 5 to 7 and palate formation during weeks 8 to 12. The absolute risk is low given that the baseline risk is 1 in 1000 live births. Prednisone also may result in premature delivery, premature membrane rupture, intrauterine growth retardation, gestational diabetes, hypertension, pre-eclampsia, and eclampsia, so many clinicians recommend prolonged use limited to 7.5 mg/day and the avoidance of >20 mg/day.^{1,41,42}

Hydroxychloroquine

Hydroxychloroquine (HCQ) is considered a first-line therapy for pregnant mothers with active lupus, and published studies have not found the maternal use of HCQ to increase the risk of congenital, neurologic, or auditory abnormalities.⁴³⁻⁴⁷ Although adults may be monitored for retinal toxicity with long-term use of HCQ, literature has not suggested similar risk in fetuses.^{48,49} In a large prospective study, those who stopped HCQ had a higher degree of lupus activity and those who continued were able to lower their prednisone dose.⁵⁰ Other beneficial effects include reducing the risk of cardiac neonatal lupus and protection against maternal osteoporosis.^{43,51} Published reviews continue to support the safety of HCQ during pregnancy.^{43,46,50}

Dapsone

Literature on dapsone, which is used extensively for leprosy and malaria chemoprophylaxis, does not indicate major fetotoxicity or congenital anomalies. Animal studies in high doses reveal that it is not a teratogen, but the tolerability of dapsone in pregnancy makes meaningful risk assessment difficult.^{52,53} Glucose-6-phosphate dehydrogenase levels should be measured before initiating therapy because of the risk of maternal anemia, and neonatal hyperbilirubinemia and hemolytic anemia have been attributed to gestational exposure.^{54,55}

Mycophenolate mofetil

Mycophenolate mofetil (MMF) was reclassified from class C to D in 2007 because the FDA acted proactively in response to postmarketing studies indicating potential increased risk of first-trimester miscarriage, microtia, external auditory canal atresia, cleft lip/palate, and finger, cardiac, renal, ocular, and central nervous system abnormalities.⁵⁶⁻⁵⁸ MMF should not be used in pregnancy, and women should use nonhormonal contraception until 6 weeks after stopping therapy, because MMF compromises the efficacy of the birth control pill.⁵⁹

Azathioprine

The main risks associated with azathioprine are preterm and low birth weight infants, and sporadic anomalies and hematologic toxicities have been reported. There are safety data supporting its use in organ transplant patients, autoimmune bowel disease, and rheumatic disease. There is no clear pattern of congenital malformation, outside of a possibly increased risk of atrial or ventricular septal defects.⁶⁰ To prevent the development of leukopenia and thrombocytopenia in newborns, a protocol was

initiated to halve the dose at 32 weeks' gestation if the mother's leukocyte count was <1 standard deviation below the mean.⁶¹ Patients taking azathioprine should not use intrauterine devices as contraception because several patients have become pregnant with their intrauterine device in place.⁶²

Intravenous immunoglobulin

Limited studies have shown intravenous immunoglobulin (IVIG) to be a safe therapy in pemphigus and pemphigoid gestationis.^{63,64} Interestingly, in patients with antibody-mediated disease—thought to contribute to up to 10% of cases of infertility—IVIG can improve the chance of in vitro fertilization resulting in pregnancy.⁶⁵ A study of anti-Ro/La⁺ pregnant women also found that IVIG was safe during pregnancy and was effective in preventing recurrent neonatal lupus.⁶⁶ Nonspecific risks specific to pooled human plasma, such as anaphylaxis, viral infections, and hypercoagulability, need to be weighed. IVIG crosses the human placenta in significant amounts only at >32 weeks' gestation and is not embryotoxic.⁶⁷

Rituximab

Rituximab is not recommended during pregnancy and has been associated with an increased risk of neonatal hematologic abnormalities. Placental passage is minimal during the first trimester, moderate during the second, and extensive during the third, and can affect fetal B-cell development. Women should be counseled to avoid pregnancy for at least 12 months after rituximab exposure.⁶⁸

SYSTEMIC ANTIPRURITICS

Antihistamines

A large number of pregnancies exposed to first-generation antihistamines have been studied, and there is no definitive increased teratogenic risk. Diphenhydramine was associated with an increased risk of cleft palate in 1 study, but this was not confirmed in multiple later studies.⁶⁹ Both chlorpheniramine and diphenhydramine are considered safe during the first trimester and are first-line agents. Exposure to hydroxyzine during the first trimester has been linked with a slightly increased risk (5.8%) of congenital anomalies.⁴¹ First-generation are preferred over second-generation antihistamines because of the preponderance of safety data. The increased risk of hypospadias initially reported with loratadine has not been confirmed in multiple subsequent studies.⁷⁰ Loratadine remains the first choice and cetirizine the second choice among second-generation antihistamines.^{10,71}

Antihistamines should be used judiciously peripartum. One study of premature infants found that the use of antihistamines within 2 weeks of delivery doubled the risk of retrosternal fibroplasia.⁷² Overdose and the intravenous use of antihistamines can stimulate uterine contractions and increase the risk of fetal hypoxia.⁷³ Withdrawal symptoms (ie, tremulousness, irritability, poor feeding, and diarrhea) have been reported in infants up to 4 weeks old with regular maternal use of antihistamines; 1 newborn developed tonic-clonic seizures with 150 mg daily maternal hydroxyzine use.^{74,75}

Doxepin

Doxepin was not teratogenic in animal models, and there are no reports definitively linking its use with human malformations. In 1 study of 118 newborns, 12 major birth defects were seen with first-trimester exposure (4.5 expected), including oral clefts, cardiovascular defects, and polydactyly.⁴¹ Antihistamines would be preferable over doxepin for pruritus during pregnancy, but human data suggest low risk.

ACNE, COSMETICS, AND SURGERY

Lidocaine and epinephrine

Both lidocaine and epinephrine are considered safe in small amounts for local anesthesia. Both cross the placenta; animal reproductive studies of lidocaine reveal no evidence of harm to the fetus, but there is 1 study that suggested an increase in malformations when mothers were exposed to systemic epinephrine during the first trimester.^{76,77} Because epinephrine's alfa-adrenergic properties may lead to vasoconstriction of placental blood vessels, fetal tachycardia, and decreased uteroplacental blood flow, the addition of this compound is not generally accepted to be of advantage in obstetric procedures.⁷⁸ However, local vasoconstriction prolongs the duration of anesthesia and reduces both maternal blood levels of lidocaine and placental transfer of lidocaine, so in dermatologic surgery the benefits of using small controlled amounts of epinephrine seem to outweigh potential risks.⁷⁸⁻⁸⁰

Minoxidil

Topical minoxidil is most frequently used as therapy for androgenetic alopecia. Concentrations in the serum are far below therapeutic levels in adults, but there have been case reports of cardiac, neurodevelopmental, gastrointestinal, renal, and limb malformations with topical use.⁸¹⁻⁸³ Because there are no conclusive studies, minoxidil is not recommended during pregnancy.

Botulinum toxin A

In general, cosmetic therapies, such as botulinum toxin A facial intramuscular injection, should be avoided during pregnancy, even though there are limited data to suggest that the risk to the fetus is low. Up to 1200 units of botulinum toxin have been used for various medical conditions without adverse effects.^{84,85} There are 5 reports of mothers with systemic botulism in the second or third trimesters, and none of the infants were affected. The only movements in a paralyzed mother were those of the fetus, so it is unlikely that the toxin crosses the placenta.⁸⁶⁻⁹⁰

Hydroquinone

Hydroquinone, a cosmetic therapy, is not recommended during pregnancy, although available data indicate low risk. Topical use results in 35% to 45% systemic absorption.⁹¹ High potency exposure in rats did not lead to increased rates of malformation.⁹² It is estimated that two-thirds of women in sub-Saharan Africa use a skin lightening agent during pregnancy; in a small cohort, hydroquinone alone without a high-potency cortisone did not increase risk of malformations, prematurity, or low birth weight.⁸

Topical retinoids

The safety data regarding adapalene and tretinoin are limited. Early case reports suggested that the use of topical tretinoin during pregnancy resulted in ear, cerebral, and cardiac malformations that are typically associated with the use of systemic retinoids in pregnancy.⁹³⁻⁹⁶ However, larger studies have not found an increased risk of retinoid embryopathy or other major birth defects with the topical use of tretinoin.⁹⁷⁻⁹⁹ Although these studies suggest that use in limited body surface area is likely safe, most experts do not recommend the topical application of tretinoin to pregnant patients.

Tazarotene

Tazarotene causes retinoid-like malformations in experimental animals, so is contraindicated in pregnancy (class X). It is highly bound to plasma protein (>99%) and maternal plasma concentrations are low, so placental transfer is unlikely. Healthy infants were delivered in several cases of inadvertent exposure.^{41,100,101}

Isotretinoin

Isotretinoin is absolutely contraindicated in pregnancy because of increased first-trimester pregnancy loss and increased birth defects, such as cleft palate, hydrocephalus, cardiac outflow tract defects, microtia, and external ear canal stenosis.¹⁰² Any patient in

the United States taking isotretinoin must enroll in iPLEDGE, a national registry that requires monthly pregnancy tests before a woman is able to obtain refills of the medication. However, numerous studies have observed that the program has not significantly decreased fetal exposure to the medication, so it is necessary to counsel patients at each visit about the dangers of becoming pregnant while taking isotretinoin.¹⁰³

Spironolactone

Spironolactone's antiandrogen effects— inhibiting 5-alfa reductase and antagonizing androgen receptors—aid in the treatment of hormonal acne and hirsutism. This medication should not be used during pregnancy because it may increase the risk of hypospadias and feminization in a male fetus.⁴¹

TOPICAL ANTIBIOTICS

In general, topical antibiotics used for skin infection, acne vulgaris, and rosacea therapy are considered safe during pregnancy. The 5% of benzoyl peroxide that is absorbed by the skin is metabolized within the skin to benzoic acid, a food additive. Exposure to benzoic acid in the diet is greater than exposure from topical application.^{101,104}

SYSTEMIC ANTIBIOTICS

Beta-lactam antibiotics

Penicillins, amoxicillin, and all cephalosporins are pregnancy class B and are considered compatible with pregnancy. Animal reproductive studies found no malformations with many times the human dose. A surveillance study revealed 317 (3.7%) malformations in 8538 newborns exposed to amoxicillin (363 expected), 27 (3.7%) in 722 exposed to cefadroxil (30 expected), and 176 (4.9%) in 3613 exposed to cephalexin (154 expected).⁴¹ Safety data support the use of amoxicillin for severe acne rosacea and cefadroxil for severe acne vulgaris. Because elimination is faster in pregnancy, it may be necessary to adjust the dose when treating infections.¹⁰⁵

Macrolides

Erythromycin, azithromycin, and clarithromycin are all second-line antibiotics to the beta-lactam antibiotics, but are considered compatible with pregnancy. Erythromycin, with data on 7000 first-trimester exposures, is the drug of choice in this class. One study indicated an increase in atrial and ventricular septal defects (1.8%) and pyloric stenosis (0.2%), but these risks are still uncertain.¹⁰⁶ Erythromycin estolate is associated with hepatotoxicity during the second trimester in 10% of

pregnancies, so erythromycin base or erythromycin ethylsuccinate should be prescribed.^{107,108}

Clindamycin

Clindamycin is compatible with pregnancy and has not been shown to increase the risk of malformation. It can cause pseudomembranous colitis with both oral and intravaginal use, so it is second-line therapy to beta-lactam antibiotics.¹⁰⁹ The laboratory must perform a D-test to rule out inducible resistance to clindamycin when treating methicillin-resistant *Staphylococcus aureus*.

Rifampin

Rifampin is not associated with an increased risk of malformations and is the treatment of choice for tuberculosis in pregnancy. Prophylactic vitamin K must be administered to infants exposed late in pregnancy to prevent hemorrhagic disease.¹¹⁰ Rifampin may interfere with efficacy of oral contraceptives.¹¹¹

Sulfonamides/Trimethoprim

Sulfonamides and trimethoprim both increased the risk of cleft palate in rats at very high doses—an effect not seen in human studies, but the combination increased the risk of cardiovascular defects with first-trimester exposure, preterm birth and low birth weight, and miscarriage.^{41,112,113} The primary danger is use near delivery, when the risk of neonatal hyperbilirubinemia increases. Trimethoprim induces folate depression in high doses or in folate-depleted individuals, so appropriate folic acid supplementation in the first trimester limits risk of NTDs.¹¹⁴

Quinolones

Quinolones should be reserved only for complicated infections, notably ciprofloxacin or norfloxacin, which have been studied the most extensively. Animal experiments indicate that quinolones can damage fetal cartilage, but they are not associated with an increased risk of malformations or musculoskeletal defects in humans.^{10,41,115}

Tetracyclines

Tetracyclines are contraindicated after 15 weeks' gestation because of maternal hepatitis, brown discoloration of deciduous teeth, and the inhibition of bone growth. Inadvertent first-trimester exposure is common and has not been associated with congenital malformations.^{10,116} There are possible associations with inguinal hernia, hypospadias, and limb hypoplasia, but no definitive patterns of malformations have been identified.⁴¹

TOPICAL ANTIFUNGALS

Extensive data regarding the intravaginal and topical application of nystatin in pregnancy do not indicate any toxic effect, so it is the drug of choice for superficial candida infection. Second-line options include clotrimazole and miconazole, which did not show embryotoxic potential.¹¹⁷ Safety data are more limited for topical ciclopirox and terbinafine. Selenium disulfide in local application for a limited period of time is acceptable.¹⁰

SYSTEMIC ANTIFUNGALS

Griseofulvin and terbinafine

Both griseofulvin and terbinafine have extremely limited safety data and are not prescribed for life-threatening infections, so neither are recommended in pregnancy. Conjoined twins were reported with griseofulvin. Teratogenicity was not seen in animal or humans with terbinafine.^{10,41,118}

Oral imidazole derivatives

First-trimester exposure of fluconazole, ketoconazole, and itraconazole increases the risk of cardiovascular, skeletal, craniofacial, and neurodevelopmental defects. Patients with first-trimester, low-dose, short-term exposure for vaginal candidiasis can be reassured that increased risk has not been shown, but they should obtain a detailed fetal ultrasound.¹¹⁹⁻¹²² Imidazoles may disrupt estrogen production in pregnancy and ketoconazole inhibits testosterone synthesis, but the effect on fetal corticosteroid synthesis is unknown.^{10,123,124}

Systemic antivirals for herpes simplex and varicella-zoster virus

Disseminated herpes simplex virus and varicella-zoster virus are important to treat intravenously during pregnancy; both are toxoplasmosis, other (syphilis, varicella-zoster, parvovirus B19), rubella, cytomegalovirus, and herpes (TORCH) infections, which potentially produce a syndrome characterized by microcephaly, sensorineural deafness, chorioretinitis, hepatosplenomegaly, and thrombocytopenia. Acyclovir is preferred because it has been studied the most extensively, although famciclovir and valacyclovir have not shown an increased risk.¹⁰ Primary herpes simplex virus and severe recurrences should be treated at 400 mg 3 times daily for 7 to 14 and 5 days, respectively. Prophylaxis can be started at 36 weeks' gestation to minimize the risk of cesarean section, but its effect on neonatal herpes incidence is unknown. Neonatal transmission risk is high (30-50%) if women acquire genital herpes near delivery and low (<1%) if

acquired in the first half of pregnancy or in women with a history of recurrent genital HSV.^{125,126}

Topical antivirals

Liquid nitrogen is safe and is a first-line treatment for warts. Trichloroacetic acid is a second-line therapy for condylomata acuminata.¹⁰ Data are limited for imiquimod, but teratogenicity has not been shown in either animals or humans.¹²⁷ Podophyllin is pregnancy class X because high doses cause heart, limb, and ear malformations, psychiatric issues, and fetal and maternal death.¹⁰ Podofilox should also be avoided, even though the risk of systemic absorption is low. Squaric acid was not a mutagen in biologic assays, but it lacks safety data in both animals and humans.¹²⁸ Cantharidin, potentially a potent tumor promoter, should be avoided since this also lacks safety data.¹²⁹

Salicylic acid

Salicylism has occurred using methyl salicylate ointments and high concentrations of salicylic acid on widespread areas of hyperkeratotic skin, but there are no known cases resulting from salicylic acid acne or wart products.¹³⁰ There is no cause for concern if used on limited areas and for limited periods of time.¹⁰

Scabies and lice

Permethrin, topical sulfur, benzyl benzoate, and crotamiton are all considered safe for scabies therapy. One case report of a pregnant woman with arachnophobia who abused aerosolized pyrethroids was associated with congenital leukemia, but no adverse effects with topical use were seen when studied.^{131,132} Benzyl benzoate was banned in the United States because its metabolite, benzyl alcohol, was associated with neonatal fatal intoxication or “gasping syndrome” from rinsing venous catheters; this has not been reported with topical use, and benzyl alcohol is available over the counter in the United States.¹⁰ Ivermectin was teratogenic in animals at high, maternally toxic doses, but no teratogenicity has been shown in humans.⁴¹ Lindane is potentially neurotoxic and should not be used. For lice, occlusive therapy with coconut oil or moisturizer is considered to be a first-line therapy.

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Safety of dermatologic medications in pregnancy and lactation

Part II. Lactation

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Learning Objectives

After completing this learning activity, participants should be able to prescribe select dermatologic medications during lactation; educate new mothers regarding the benefits and potential risks of taking select dermatologic medications during lactation; and appropriately monitor for side effects in new mothers and infants when administering select dermatologic medications during lactation.

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Dermatologists are frequently faced with questions from women who are breastfeeding about the safety of commonly prescribed topical and systemic medications during lactation. Safety data in lactation, particularly regarding medications that are unique to dermatology, are limited and can be difficult to locate. We have consolidated the available safety data in a single reference guide for clinicians. We review literature pertaining to the safety of common dermatologic therapies in lactation and offer recommendations based on the available evidence. (J Am Acad Dermatol 2014;70:417.e1-10.)

Key words: acne; antibiotic; antifungal; antihistamines; antiviral; atopic dermatitis; biologics; breastfeeding; breast milk; corticosteroid; cosmetics; eczema; lactation; medication safety; nursing; phototherapy; psoriasis; surgery.

TOPICAL ANTIINFLAMMATORY DRUGS IN PREGNANCY

Corticosteroids

Corticosteroids are a normal component of breast milk, with a mean average concentration of 7 µg/L.¹ Topical corticosteroids can be used safely in lactation, and infant exposure through milk is minimal.² There was a case of iatrogenic hypertension in an infant exposed to high potency topical corticosteroids applied directly to the nipple.³ Consequently, high potency steroids should not be used directly on the nipple.⁴

Calcineurin inhibitors

When used topically, these medications are poorly absorbed systemically because their molecular size prevents penetration. Even when administered orally, tacrolimus transmission into breast milk was minimal, and infant serum levels were very low or nonexistent.⁵ The published literature reveals that infants exposed to the medications had no adverse effects or increased infections, and met all developmental milestones.⁶⁻⁸ The level of exposure through lactation is far less than what is used safely for infantile organ rejection, yet the potential effects of exposure through milk are unknown, which is why manufacturers state that tacrolimus is

Abbreviations used:

AAP:	American Academy of Pediatrics
MTX:	methotrexate
MMF:	mycophenolate mofetil
WHO:	World Health Organization

contraindicated during lactation. This recommendation does not specify topical or systemic use. Topical use should be approached with caution. Tacrolimus and pimecrolimus should be used sparingly and not directly on the nipple, because oral absorption in the infant could be significant.

Coal tar

Animal studies have shown that exposure in utero to high-dose coal products resulted in perinatal mortality, an increased risk of cleft palates, and small lungs in offspring, but the literature on human exposure has failed to reveal any developmental effects.^{9,10} One case examined the use of topical coal tar products in a breastfeeding woman and analyzed both the breast milk concentrations and infant urine concentrations. Interestingly, levels of the coal tar's active molecules were detected in the infant's urine, but none were detected in the milk itself. This led the

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authors to conclude that most of the exposure to the coal tar came via skin-to-skin or skin-to-mouth contact between mother and infant.¹¹ The nature of coal tar application often involves the majority of a patient's body surface area, making it difficult to completely prevent direct fetal exposure. It is recommended that mothers avoid the use of coal tar while breastfeeding.

Calcipotriene

Calcipotriene is a vitamin D analog, and because vitamin D is a normal component of breast milk, potential excessive vitamin D exposure could result in D-hypervitaminosis. However, when used only in localized areas, there is minimal risk of significant systemic absorption. Vitamin D is secreted into milk in limited concentrations and is proportional to maternal serum levels.¹² Excessive doses can produce elevated calcium levels in the infant, so doses <10,000 IU/day are suggested.¹³ Calcipotriene is compatible with breastfeeding.¹⁴

SYSTEMIC THERAPY FOR PSORIASIS

Methotrexate

Methotrexate (MTX) is transferred into milk, and literature reveals the highest milk to plasma concentrations at 10 hours postingestion. Although there are significantly decreased concentrations of MTX in breast milk compared to maternal serum, MTX is believed to be retained in human tissues for months, particularly neonatal gastrointestinal cells and ovarian cells, and there is concern regarding toxic accumulation secondary to immature renal function. MTX is contraindicated during lactation.¹⁵

Cyclosporine

The published literature shows that cyclosporine is available in breast milk at variable levels. In 7 cases of neonatal exposure through lactation, there was no observed nephrotoxic effect monitored with creatinine levels from week 1 through the end of breastfeeding. In addition, there was no observed damage to the thymus, which had been reported in previous animal studies.¹⁶ While there are cases reported of safe infant exposure during lactation with normal growth, development and absence of other adverse reactions, the American Academy of Pediatrics (AAP) and other clinical groups identify cyclosporine as cytotoxic and recommend avoidance of the medication during lactation.¹⁶⁻²¹ In cases where the mother

elects to breastfeed, the infant needs to be monitored for symptoms of cyclosporine toxicity, including edema, tremor, hirsutism, hypertension, and seizure,⁴ and infant plasma levels should be followed closely.⁴

Biologic tumor necrosis factor-alfa inhibitors

Immunoglobulin G (IgG) transfer into human milk is significant the first 4 days postpartum and minimal afterward. The primary immunoglobulin in mature human milk is IgA. Immunoglobulins are transferred into human milk by a very specific carrier protein that inhibits the transfer of IgG-like products. It is not known if these unusual immunoglobulins are transferred into milk, but because of the enormous molecular weight of the tumor necrosis factor-alfa inhibitors (etanercept is 150,000 Daltons, for example), it is extremely unlikely that clinically relevant amounts would transfer into milk in breastfeeding mothers.⁴ Etanercept is found only in extremely small concentrations in breast milk and is undetectable in the sera of breastfed children.^{22,23} Absorption is also minimal because the infant's digestive acids and enzymes break down the medication's protein structure.²⁴ In all reported cases of the use of etanercept in lactation, the child reached developmental milestones.^{22,25} Case reports regarding the use of adalimumab during lactation show no adverse effects in the infant.²⁶ Similarly, a case series of infliximab revealed no detectable drug concentrations in breast milk, no adverse effects, and normal fetal development.^{27,28} The biologic medications are likely compatible for use while breastfeeding.

Acitretin

While the literature shows minimal transfer into breast milk of acitretin and the American Academy of Pediatrics suggests compatibility, the medication should be avoided during lactation because of the potential for cumulative toxicity.^{19,29} Infants may be unable to clear the drug via immature renal and hepatic systems. This could potentially elevate the drug to unsafe levels, and hypervitaminosis A in infants predisposes to retinoid toxicities, including hepatotoxicity, increased intracranial pressure, bone and joint pain, and an increased risk of respiratory infection.³⁰

PHOTOTHERAPY

Ultraviolet light therapy

Narrowband and broadband ultraviolet B therapy is considered compatible during lactation. No

adverse effects have been reported from the use of either therapy.³¹

Psoralen plus ultraviolet A light phototherapy

Psoralen plus ultraviolet A light phototherapy is administered both in oral capsules and as a topical lotion. While topical application minimizes systemic exposure, its transfer into breast milk is unknown. However, because of the potent photosensitizing effects of psoralen plus ultraviolet A light phototherapy, breastfeeding should be avoided for at least 24 hours until 95% has been cleared through the mother's urine, because the drug will enter and exit the milk as a function of the mother's plasma level.^{14,32,31} Other forms of phototherapy should be preferentially used before psoralen plus ultraviolet A light phototherapy is considered.

OTHER SYSTEMIC ANTIINFLAMMATORY DRUGS

Systemic corticosteroids

The AAP considers systemic corticosteroids "usually compatible" for lactation and recommend prednisone or prednisolone over other options.¹⁹ Prednisone is metabolized to prednisolone, and studies show small amounts of the metabolite are transferred to milk.^{33,34} For mothers with doses between 10 mg and 80 mg, relative infant doses ranged from 0.02% to 0.074% (0.002-0.059 mg), which represents <10% of the infant's endogenous cortisol level.³⁵ The published literature fails to show adverse effects in lactating infants, although these studies include modest maternal doses (between 5-10 mg daily).^{16,17,36,37} In an effort to minimize exposure and avoid peak levels occurring 1 hour after ingestion, it is recommended that mothers wait to breastfeed 4 hours after ingestion, because the concentration within the milk will fall with the maternal plasma level.^{4,38}

Hydroxychloroquine

While hydroxychloroquine is considered a first-line therapy for pregnant mothers with active lupus, controversy exists for its use during lactation. Cases reveal safe use with minimal exposure to the infant through breast milk, with exposure ranging from 0.005% to 0.35%.^{39,40} The theoretical infant dose has been estimated to be 0.16 mg/kg/day with a relative infant dose of 2.9%. As a point of comparison, the pediatric dose for malaria prophylaxis is 5 mg/kg/week. The concern regarding the medication lies in its slow elimination rate; therefore, a theoretical risk exists of toxic collection within the infant. While the 1988 World Health Organization (WHO) recommendations specify that women using the medication for connective tissue diseases should avoided

breastfeeding, more recent 1992 AAP guidelines consider it safe during lactation.^{14,19,41}

Dapsone

Dapsone and its primary metabolite, monoacetyl-dapsone, can be found at high relative concentrations in breast milk, with the maximum reported at 14.3% the maternal dose.⁴² There is 1 report of an infant developing hemolytic anemia from exposure through breast milk.⁴³ Dapsone's long half-life of 20 hours puts infants at risk of accumulation; therefore, the WHO⁴¹ concluded that dapsone was unsafe for breastfeeding.¹⁴ The AAP indicates that infants at risk of hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency should avoid exposure.¹⁹

Mycophenolate mofetil

Animal studies show a significant transfer of mycophenolate mofetil (MMF) into the milk of lactating rats, likely because of its low molecular weight.⁴⁴ This potential exposure could lead to adverse effects on neonatal development and an increased frequency of infection and lymphoma. The potential risks are significant enough that MMF is contraindicated during lactation.¹⁴

Azathioprine

The 1988 WHO Group report titled *Drugs and Human Lactation* recommended against the use of azathioprine while breastfeeding.⁴¹ Since that time, several studies have shown that azathioprine and its metabolites were undetectable or in very low concentrations in breast milk.^{45,46} In addition, case series have shown successful use during lactation at maternal doses as high as 175 mg/day.^{47,48} One abstract reported discontinuation of breastfeeding in 1 of 6 mothers because of a decline in the child's white blood cell count. While the older recommendations advise avoidance, data over the last 25 years suggest that azathioprine may be compatible with breastfeeding. It is recommended to wait 4 hours after ingesting the medication because the majority of exposure occurs within the first 4 hours, and to periodically check infant blood counts.^{46,49}

Intravenous immunoglobulin

The literature regarding lactation and intravenous immunoglobulin comes from patients with multiple sclerosis. Studies show that protein immunoglobulins are transferred into milk, but they did not result in consistent or significant adverse effects.⁵⁰ The largest cohort included 69 women, and no adverse effects were recorded amongst the breastfed infants.⁵¹ Therefore, while there is infantile exposure, intravenous immunoglobulin can be used safely.

Rituximab

Rituximab, an IgG antibody that binds to the CD20 antigen found on B lymphocytes, is regularly excreted into milk the first 14 days postpartum and is present in small amounts in breast milk thereafter. Although oral bioavailability is likely negligible, it may have a negative effect on the infant's developing gastrointestinal tract. Rituximab should be avoided during lactation, but, if used, the infant's B cell count must be periodically monitored.

SYSTEMIC ANTIPRURITICS

First-generation antihistamines

First-generation antihistamines are known for their sedating effects because of their ability to easily cross the blood–brain barrier. There is a theoretical risk that the sedating effects could increase the risk of sudden infant death syndrome, but the published literature fails to show this association. One large study looking at breastfed children of mothers taking chlorpheniramine and diphenhydramine observed short-lived irritability and drowsiness but no major adverse effects.³⁶ Another study looked at lactating females taking antihistamines for seasonal allergies and found that 22.6% of mothers reported perceived irritability, drowsiness, or decreased sleep in their neonate, but none required medical attention.⁵²

There is also a theoretical risk of central acting histamine blockade altering milk production because of effects on the dopamine regulatory system. This, too, remains theoretical given that multiple studies have shown that antihistamines do not affect milk production.^{53,54}

First-generation antihistamines should be used with caution, and parents should be counseled to monitor children for signs of irritability or drowsiness. Nonsedating, second-generation antihistamines are preferred.

Second-generation antihistamines

Second-generation antihistamines do not cross the blood–brain barrier as readily, and therefore minimize the central sedating effects. Transfer of cetirizine, fexofenadine, and loratadine are reported as low as 3.0%, 0.1%, and 1.1% of the maternal dose, respectively.^{4,55,56} These levels of exposure are unlikely to result in clinical effects, so the AAP has labeled second-generation antihistamines compatible for lactating mothers.¹⁹ Nevertheless, for mothers consuming high doses of the medication, signs of excessive irritability, jitteriness, and drowsiness should be considered grounds for discontinuation.

Doxepin

Doxepin and its active metabolite are excreted into human milk.^{57,58} While the transfer is small, studies show that exposed infants experienced poor suck, poor swallowing, muscle hypotonia, and emesis. The symptoms diminish <2 days after the last feed.⁵⁹ There is 1 report of an infant developing dangerous sedation and respiratory arrest.⁵⁷ With these data, the WHO classifies doxepin as incompatible with breastfeeding.⁴¹

ACNE, COSMETICS, AND SURGERY

Lidocaine

Lidocaine is most frequently used in dermatology as a local anesthetic, but data pertaining to its excretion in milk come from alternative uses in obstetric and cardiac literature where doses are generally higher. Milk concentrations in 27 epidural cases were low and dropped significantly within 12 hours after administration.⁶⁰ No adverse effects were observed, and the AAP classifies lidocaine as compatible with lactation.¹⁹

Epinephrine

Epinephrine is used with lidocaine to improve the localization via vasoconstriction. The standard dilution of 1:50,000 or 1:100,000 confers minimal exposure. When used at such low doses, it is not associated with impaired lactation.^{61,62}

Minoxidil

Minoxidil is most frequently used topically for androgenetic alopecia, and only 1.4% of the dose is absorbed systemically. The AAP classified the topical use of minoxidil as compatible with lactation.¹⁹

Botulinum toxin A

It is recommended generally to avoid cosmetic therapy during breastfeeding, although systemic exposure is unlikely from local intramuscular injections of botulinum toxin A and poses minimal risk to a nursing infant. One case of a mother paralyzed by systemic botulism revealed detectable levels of the toxin in serum but not in her breast milk. Throughout the hospitalization, the infant was able to breastfeed without symptoms or detection of the toxin in infantile serum.⁶³

Hydroquinone

The transcutaneous absorption of hydroquinone is reported to be about 35%, and the medication distributes rapidly and widely. Because it is more ionic, it can be less capable of transferring from the milk to the maternal plasma and can become trapped in milk. Although it does not appear to be highly

risky or toxic, it is difficult to justify chronic use in a breastfeeding mother.⁴

Topical tretinoin

Because vitamin A is a normal component of breast milk, tretinoin is likely to be excreted in breast milk. However, the topical formulation is unlikely to be absorbed in significant quantities, thus it is likely safe during lactation.^{64,65}

Spironolactone

Spironolactone's active metabolite canrenoate is detected at 0.2% of the maternal dose.⁶⁶ Both the AAP and the WHO classify spironolactone as compatible with lactation. Suppression of milk supply is possible but unlikely.^{19,67}

Tazarotene

When used topically, the systemic absorption is estimated to be 6%.⁶⁸ Tazarotene is a prodrug that is metabolized to its active form tazarotenic acid, which is less lipophilic than other retinoids, lessening its risk for transfer to milk.⁶⁹ However, trace amounts of tazarotene are excreted into milk, and some caution is recommended if used over large surface areas (20-30%).⁴

Isotretinoin

The elective use of isotretinoin is contraindicated during lactation because isotretinoin is extremely lipid soluble and concentrations in milk would be significant. The risk of retinoid toxicity in the infant is too high to use in a breastfeeding woman.⁴

SYSTEMIC ANTIBIOTICS

Antibiotics

Lactating mothers taking antibiotics should be counseled to watch for hypersensitivity reactions in infants and signs of gut flora changes, such as diarrhea, dehydration, or candidiasis.

Penicillins and cephalosporins

The potential acute and long-term toxic effects of these classes on breastfeeding have been well studied. Their concentrations in human milk are <1% of the weight-adjusted maternal dose.^{70,71-73} Both penicillin and cephalosporins can be safely used during lactation.^{19,41}

Macrolides

Erythromycin, azithromycin, and clarithromycin are all transferred into breast milk at minimal concentrations.⁷⁴⁻⁷⁶ While all 3 medications are considered compatible for lactation, there are additional considerations. Two studies indicated a possible association

between the use of erythromycin during lactation and an increased risk of infantile hypertrophic pyloric stenosis^{77,78}; however, a follow-up study failed to find any association between erythromycin and infantile hypertrophic pyloric stenosis.⁷⁹ The AAP and the WHO both maintain erythromycin is safe, but short-term use is recommended.^{19,41} Azithromycin has the longest half-life and confers the largest relative infant dose (10.1%), but studies have not noted any adverse effects.⁸⁰ Clarithromycin is safe and used therapeutically in infants at much higher doses (7.5 mg/kg) than breastfed infants would be exposed to through milk. Studies have failed to show any adverse effects caused by infant exposure.^{4,79}

Clindamycin

Clindamycin reaches breast milk in small concentrations and is deemed safe for lactation by the AAP.^{19,81} There is 1 case describing an infant's exposure through breast milk and subsequent development of bloody stools. However, the mother was taking several antibiotics concurrently, and the baby reportedly "appeared well" while stool cultures were negative and showed "normal flora." There was no recurrence of gastrointestinal issues once the child restarted breastfeeding.⁸²

Rifampin

Breastfeeding infants exposed to rifampin are likely to ingest 0.05% of the maternal daily dose.⁸³ This minuscule exposure has failed to result in adverse effects, and rifampin is considered safe.^{19,84} In addition, children were followed 5 years after exposure during lactation and had normal development.⁸⁵

Sulfonamides/trimethoprim

Sulfonamides are transferred into breast milk at low enough levels where clinical effects are unlikely.⁸⁶ The AAP classifies sulfonamides as safe during pregnancy, but they should be avoided in premature infants or neonates with hyperbilirubinemia or glucose-6-phosphate dehydrogenase deficiency. The medications can displace bilirubin from albumin, which worsens hyperbilirubinemia.¹⁹ Sulfamethoxazole is commonly used in combination with trimethoprim, which has higher relative infant doses.^{19,36,87}

Quinolones

For many years, the theoretical risk of arthropathy prevented the use of this class of drugs, but the published literature does not show this association for exposure during lactation. Most literature examining ciprofloxacin finds that when digested with milk, the exposure is far below pediatric doses.^{88,89} One theory is that the ionized calcium in breast milk compromises the absorption of the medication.⁴

With the unproven concern regarding arthropathy and only 1 case of pseudomembranous colitis in an exposed breastfed infant, the AAP considers ciprofloxacin safe for lactation.^{19,90} In addition, other quinolones, including ofloxacin, levofloxacin, and norfloxacin, consistently show lower concentrations in breast milk than ciprofloxacin.⁴

Tetracyclines

Much like the quinolones, the theoretical risks of tetracyclines have limited their use. The published literature fails to show an association between exposure through breastfeeding and a negative impact on tooth or bone growth. Studies show the exposed dose is low, and the bioavailability in milk is limited because of calcium chelation.^{71,91,92} Studies do not show any adverse reactions for infants exposed during lactation short-term.^{4,93} The AAP and WHO consider tetracyclines compatible with lactation, but the medication should not be used for >3 weeks because when consumed over an extended period, the absorption of even small amounts over a prolonged period could result in dental staining.^{4,19,41}

TOPICAL ANTIFUNGALS

Undetectable amounts of nystatin were found in maternal serum when given orally because of the medication's poor bioavailability.⁹⁴ Similarly, when applied to the skin or vaginal mucosa, the systemic absorption of clotrimazole is minimal.¹⁴ Ciclopirox systemic absorption is only 1.3% even when applied with occlusion. In addition, <5% of topical terbinafine is absorbed systemically. Topical antifungals are all likely safe in lactation.¹⁴

Selenium is an essential element that is normally excreted in breast milk. There is concern that excessive exposure can suppress milk production, but animal studies looking at toxic level exposures showed no significant changes.⁹⁵ In the 1 reported case of lactation suppression, levels returned to normal after discontinuation of the treatment.⁹⁶ There are no reported cases of adverse effects when used during lactation.

SYSTEMIC ANTIFUNGALS

Griseofulvin

Griseofulvin has tumorigenic potential and could hamper neonatal development. Griseofulvin should be avoided while breastfeeding.^{14,97}

Oral imidazole derivatives

Pediatricians frequently use fluconazole in neonatal populations where it is proven safe.⁹⁸ High concentrations of fluconazole are found in breast milk at approximately 16% of the maternal

dose, but the exposure remains far below the standard intravenous doses safely given to neonates.⁹⁹ No adverse reactions were noted when given to preterm infants for 6 weeks; exposure in milk is therefore considered safe.¹⁰⁰

Ketoconazole and itraconazole require acidic conditions to be absorbed, and because milk is alkaline, they are both absorbed poorly in milk. Ketoconazole exposure was measured at 1.4% the maternal dose.¹⁰¹ The AAP classifies ketoconazole as safe to use while lactating.¹⁹ On the other hand, itraconazole may concentrate within nursing infants, so while there are no reports of adverse effects from exposure through breast milk, alternative imidazole derivatives are preferred.¹⁴

Terbinafine

Terbinafine is transferred to human milk, and the child receives about 4% the maternal dose.^{102,103} Given that the medication is prescribed for long periods of time, while there are no human data detailing infantile toxicities, the risk is high enough to recommend avoidance during lactation.¹⁴

Systemic antivirals for herpes simplex and zoster

The published literature shows transfer of acyclovir into breast milk with infantile exposure between 1% to 8.5% the maternal dose.^{104,105} These levels of exposure are presumed to be both subtoxic and subtherapeutic.¹⁰⁶ Cases of neonatal exposure have failed to show adverse effects, and the AAP classifies the medication as safe.^{19,104,107}

Valacyclovir is a prodrug and is quickly converted into acyclovir, which is transferred into milk at low quantities; the relative infant dose is 2.4%.¹⁰⁸ In contrast, famciclovir has greater bioavailability, and animal studies show concentrated levels in rat milk. Current recommendations suggest the preferential use of acyclovir or valacyclovir.⁴

Topical antivirals (warts)

The use of liquid nitrogen is safe during breastfeeding. Topical salicylic acid, as a keratolytic, is used locally for the treatment of warts. Systemic absorption of the medication is minimal, and the American Academy of Dermatology considers both as preferential therapies while breastfeeding.¹⁰⁹

Scabies and lice

Permethrin is the preferred treatment for lice and scabies during lactation. When administered topically, there is minimal systemic exposure for both permethrin and pyrethrins, and both are considered

safe during lactation by the Centers for Disease Control and Prevention 1998 guidelines.¹¹⁰ Permethrin has been used safely directly on infants >2 months of age.¹¹¹ The AAP considers ivermectin compatible for lactating mothers when topical therapies are ineffective.¹⁹ Relative infant doses are as low as 0.98%.^{4,112} Benzyl benzoate is commonly used in Europe for scabies, but it is not available in the United States.^{4,111}

Lindane and malathion are 2 medications to avoid during lactation. Lindane is well absorbed systemically and detected in milk.¹¹¹ Its exposure in breastfeeding infants can result in seizures and elevated liver function tests, thereby precluding its use.¹¹³ Malathion is reported to be associated with respiratory depression in exposed neonates. Maternal topical absorption is <10% on the scalp. The infant should not be exposed directly, and the infant should not breastfeed if the mother develops symptoms such as lacrimation, salivation, or shortness of breath after use.¹¹⁴

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Electrosurgery

Part I. Basics and principles

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After completing this learning activity, participants should be able to list the various electrosurgical modalities and describe their indications and contraindications; delineate the tissue effects of various electrical waveforms; recognize the factors influencing depth of tissue injury; and identify the sources of possible complications and describe strategies for the prevention of these complications.

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The term electrosurgery (also called radiofrequency surgery) refers to the passage of high-frequency alternating electrical current through the tissue in order to achieve a specific surgical effect. Although the mechanism behind electrosurgery is not completely understood, heat production and thermal tissue damage is responsible for at least the majority—if not all—of the tissue effects in electrosurgery. Adjacent to the active electrode, tissue resistance to the passage of current converts electrical energy to heat. The only variable that determines the final tissue effects of a current is the depth and the rate at which heat is produced. Electrocoagulation occurs when tissue is heated below the boiling point and undergoes thermal denaturation. An additional slow increase in temperature leads to vaporization of the water content in the coagulated tissue and tissue drying, a process called desiccation. A sudden increase in tissue temperature above the boiling point causes rapid explosive vaporization of the water content in the tissue adjacent to the electrode, which leads to tissue fragmentation and cutting. (J Am Acad Dermatol 2014;70:591.e1-14.)

Key words: coagulation; current; electricity; electrocoagulation; electrodesiccation; electrofulguration; electrosurgery; high frequency; radiofrequency.

INTRODUCTION

Key points

- In electrosurgery, an electric current flows from the active electrode through the patient's body to the return electrode
- Electrocautery differs from electrosurgery in that an electrical current heats a metallic probe that is then applied to tissue (hot iron cautery). Because no heat is generated in deeper tissue, electrocautery is more suitable for the destruction of superficial tissue layers

The concept of using heat for hemostasis goes back hundreds of years. As technology evolved, devices were created that used electricity to heat tissue and control bleeding. These advancements eventually developed into modern-day electrosurgery. The term electrosurgery (also called radiofrequency surgery) refers to the passage of high-frequency electrical current through the tissue in order to achieve a specific surgical effect, such as cutting or coagulation (Table 1). Each electrosurgical device consists of a high frequency electrical generator and 2 electrodes (Fig 1). The electric current flows from the active electrode through the patient's body and then to the return (dispersive) electrode,

where current flows back to the electrosurgical generator. Adjacent to the active electrode, tissue resistance to the passage of alternating current converts electrical energy to heat, resulting in thermal tissue damage. While heat generation occurs within the tissue, the treatment electrode acts as a conductor that only passes the current and may remain cooler than the treated medium.^{1,2} Electrocautery differs from electrosurgery in that an electrical current heats a metallic probe that is then applied to tissue (hot iron cautery). In electrocautery, no current flows through the patient's body (Fig 2).³ Because no heat is generated in deeper tissue, electrocautery is more suitable for the destruction of superficial tissue layers.

The term diathermy was originally applied to the therapeutic (nonablative) heating effect of passing high-frequency electrical current through deeper parts of the body. This term was later used to describe cutting tissue.^{4,5} While the term diathermy is still used today, the term electrosurgery is preferred when referring to cutting or coagulation.

Although electrosurgical instruments are used routinely, familiarity with the principles behind how these instruments produce their effect is limited.^{6,7} An understanding of the basic principles of electrosurgery can help increase efficiency of use and reduce complications.

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Table I. Electrosurgical modes and definition of common terms used in electrosurgery

Method	Electrical current or mode of choice	Alternative currents	Definition
Electrocautery	Direct current	Alternating current	An electrical current heats a metallic probe that is then applied to tissue
Electrosurgery	High-frequency alternating current	—	A high-frequency electrical current is passed through the tissue in order to achieve a specific surgical (thermal) effect, such as cutting or coagulation
Electrocoagulation (contact coagulation)	Continuous current (cutting mode)*	Interrupted currents (eg, blend, coagulation, or fulguration modes)	The tissue is heated below the boiling point and undergoes thermal denaturation
Electrodesiccation	Same as electrocoagulation	Same as electrocoagulation	Vaporization of the water content and drying occurs at superficial tissue layers at the end of coagulation
Electrofulguration (spray or noncontact coagulation)	Interrupted current (fulguration mode)	Interrupted current (coagulation mode)	The active electrode is held a few millimeters above the tissue. The electric current bridges the air gap by creating a spark
Electrosection, pure cutting	Continuous current (cutting mode)	—	A sudden increase in tissue temperature above the boiling point leads to tissue fragmentation and cutting. In pure cutting, there is little coagulation on the incision walls and little hemostasis
Electrosection, blend cutting	Interrupted current (blend or coagulation modes)	—	In blend cutting, there is more coagulation on the incision walls and more hemostasis than pure cutting
Bipolar electrosurgery	Bipolar mode	—	There are 2 active electrodes
Monopolar electrosurgery	Monopolar modes (for cutting, coagulation, desiccation, and fulguration)	—	There is 1 active and 1 dispersive (return) electrode
Biterminal electrosurgery	All modes (for cutting, coagulation, desiccation, and fulguration)	—	Both active and return electrodes are in contact with the patient's body
Monoterminal electrosurgery	All modes except for pure cutting (monoterminal mode is not suitable for pure cutting)	—	Return electrode is not connected directly to the patient's body; instead, it is connected to the Earth and the Earth acts as an indirect return electrode

*The cutting mode in some electrosurgical units cannot provide a very low power output that is necessary for a superficial coagulation using a fine-tip electrode.

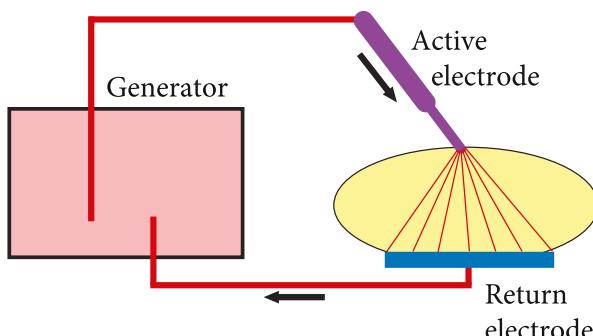


Fig 1. An electrosurgery circuit. Current flows through the tissue, generating heat within the tissue. Heat generation is practically limited to the area of high current density, meaning adjacent to the active electrode. The characteristics of the current flow affect the depth, speed, and degree of tissue heating and determine the tissue results. The arrows indicate the direction of the electricity in 1 phase of current. In the next phase, the current will be in the opposite direction.

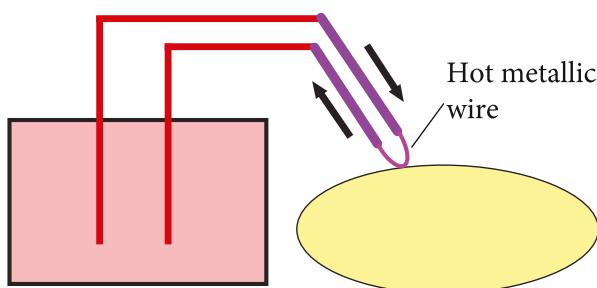


Fig 2. An electrocautery circuit. No current flows through the patient's body. Current heats the tip of the probe, which can then be used to heat superficial tissue layers.

FUNDAMENTALS OF ELECTRICITY

Key points

- In a high-frequency alternate current circuit, cables and pathways of electricity always form capacitors with each other and with nearby conductive environmental objects. Therefore, all insulation on instruments and cables is relative and some energy always leaks through it as a capacitive current
- If the active electrode cable comes in close proximity to the patient's body, current leakage may result in a burn
- When a direct or low-frequency current enters the body, a chemical reaction called electrolysis occurs at the electrode–tissue interface. The chemical effects of electrolysis disappear at higher frequencies
- A direct or low frequency current can depolarize cell membranes and cause neuromuscular excitation. Neuromuscular stimulation becomes negligible at higher frequencies

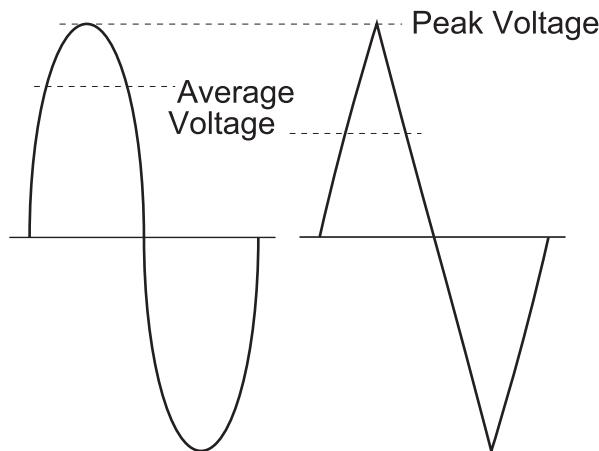


Fig 3. The peak and average voltage of alternating electrical currents. The left waveform has a higher ratio of average to peak voltage than the right waveform.

Electricity and currents

There are 2 types of electrical current: direct and alternating. Direct current uses a simple circuit and flows only in 1 direction, whereas alternating current switches, or alternates, the direction of the flow of electricity back and forth. Household electrical wall outlets, for example, have alternating currents. During each phase of an alternating current, voltage and current fluctuate between a maximum (peak) and a minimum (0). The effective or average voltage is lower than the peak voltage (Fig 3) and is usually used to describe an alternate current source and to calculate the power.

A continuous circuit must be present in order for a direct current to flow. However, an alternating current can pass through some breaks and insulations by several mechanisms, the most important of which is capacitance. In its simplest form, a capacitor consists of 2 nearby conducting plates separated by a nonconducting medium (Fig 4). Higher frequency alternating currents can pass a capacitor more easily than lower frequency alternating currents. The flow of an alternating current through a capacitor is known as a capacitive current. In an alternate current circuit, cables and pathways of electricity always form capacitors with each other and with nearby conductive environmental objects. Therefore, high-frequency alternating currents are impossible to insulate completely. All insulation on instruments and cables is relative, and some energy always leaks through insulations as capacitive current.^{8,9}

In an electrosurgery circuit, the tissue adjacent to the active electrode acts as a resistor that induces heating (Fig 1). If the active electrode cable comes in close proximity to the dispersive electrode cable or

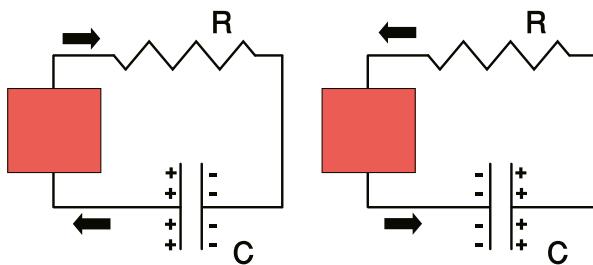


Fig 4. An alternate current circuit with a generator, a resistor (R), and a capacitor (C). A capacitor consists of 2 nearby conducting plates separated by a nonconducting medium. When a direct current voltage source is applied to a capacitor, there is an initial surge of current. Electrons flow into 1 of the plates, giving it a negative charge, and are taken off the other plate, causing that plate to become positively charged. While the capacitor is charging, current flows, usually for a fraction of a second. The current will stop flowing when the capacitor has fully charged. However, if the current changes its direction, as in the case of an alternating current, the current will flow and charge the capacitor every time the electricity changes direction. Therefore, some current will be allowed to pass in each phase of the cycle. As the frequency of alternations increases, more current passes the capacitor every second. The result is that higher frequency alternating currents can pass the capacitor more easily than lower frequency alternating currents.

to the patient's body, a capacitor is formed that passes some of the current through an alternate path (**Fig 5**). This is called current leakage.¹⁰ Current leakage may result in a burn on the patient or anyone that comes in contact with the cable (**Fig 5**).¹¹

As detailed earlier, higher frequency alternating currents can pass the capacitors more easily than lower frequency currents. Ultra-high frequencies (>5 MHz) are not used in electrosurgery because the leakage effect is too great to fall within the limits set by safety standards.^{12,13}

Electricity and biologic tissues

Electrical conduction differs depending on the conductive material. In metals, the charge carriers are primarily electrons, whereas in gases and liquids the carriers are ions.^{14,15} Gases are nonconductive materials. When a nonconductive gas is placed in a sufficiently high voltage electric field (eg, between the 2 poles of a high-voltage generator), the gas will be ionized. This ionized gas is called plasma and conducts the electrical current as a spark. Two common examples of plasma are lightning in nature and fulguration in electrosurgery.

Electrical conduction in biologic tissues is primarily caused by the conductivity of body fluids and is therefore predominantly ionic.^{16,17}

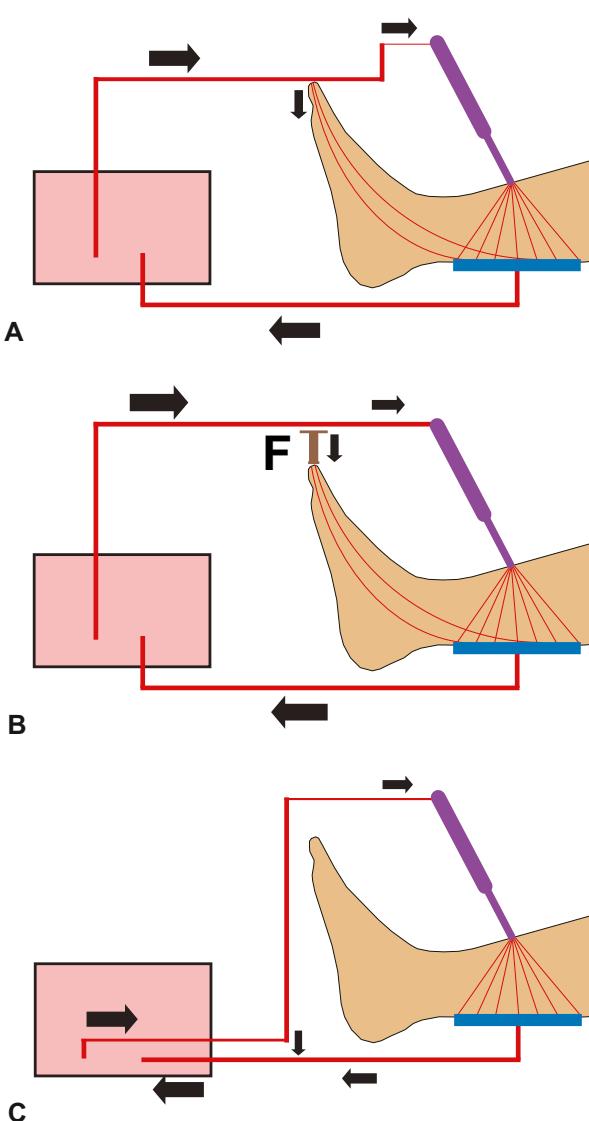


Fig 5. Current leakage in electrosurgery circuit. Current leakage from active electrode cable to the patient's body may result in a burn. It can occur as a result of putting the active cable near the patient's body (**A**) or near any conductive element that is in direct contact or close contact to the patient's body or surgical staff (**B**; object F). Examples of object F can be a surgical table or a metallic clamp that is used for securing the cable to the surgical drapes over the patient's body. On the other hand, if the active and dispersive electrode cables are put near each other, current will leak from the active to dispersive electrode cable before reaching the active electrode (**C**). As a result of this power loss, the power dissipated in tissue will be less than the output power of the generator.

Chemical effects of electrical currents on tissues

When a direct current enters the body through a metallic electrode, a chemical reaction called

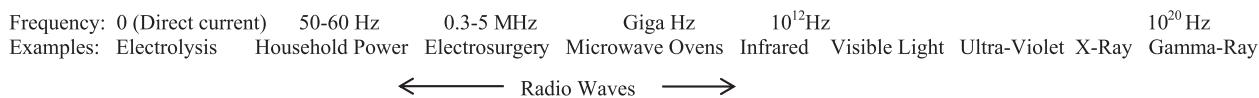


Fig 6. Electromagnetic spectrum. Electrosurgical units use alternating currents with frequencies which are part of the radio-wave frequency range.

electrolysis occurs at the electrode–tissue interface. This chemical reaction may cause destruction of a thin layer of tissue around the electrode very slowly.¹⁸ Electrolysis has been used as a method of hair removal (galvanic depilation) and for the treatment of telangiectasia.¹⁹⁻²¹ A low-frequency alternating current can cause similar chemical reactions. However, because the chemical reaction of each phase can be neutralized by the opposite phase, these chemical effects diminish as the frequency of alternations increase and almost disappear at high frequencies (>5 to 10 kHz).^{2,17,22-26}

Effects of electrical currents on cell membranes

A direct or low-frequency alternate current can depolarize cell membranes and cause neuromuscular excitation. This stimulation may cause pain, muscle contraction, and even cardiac arrhythmia. Neuromuscular stimulation decreases as the frequency of current increases above 1 kHz, and becomes negligible at frequencies of 100 to 300 kHz.^{22,23,26-28} At these high frequencies, current reversal is so rapid that cellular ion position change is essentially nil and depolarization fails to occur. High-frequency alternating current therefore makes it possible to exploit the heating effects of electricity while avoiding the undesirable neuromuscular effects. Whereas physiologic reasons dictate the lower limit of the frequency used, as detailed earlier, practical and safety considerations place restrictions on the upper limit of current frequency used by electrosurgical units. Electrosurgical units typically produce alternating currents in the frequency range of 0.3 to 5 MHz. These frequencies are part of the radiowave frequency range (Fig 6); this is why electrosurgery is also called radiofrequency (RF) surgery or high-frequency electrosurgery. Although these terms are used synonymously, the term electrosurgery has a more specific meaning in applied biomedical engineering and is the preferred term.^{10,29,30}

BASIC MECHANISM OF ELECTROSURGERY

Key points

- An active electrode can concentrate the current at a small area and provide a sufficiently

high current density to induce heating and thermal tissue damage. The large return electrode disperses the current, reducing the current density to levels where tissue heating is minimal

- **Electrocoagulation occurs when tissue is heated below the boiling point and undergoes thermal denaturation**
- **An additional slow increase in temperature leads to vaporization of the water content and tissue drying, a process called desiccation**
- **A sudden increase in tissue temperature above the boiling point causes rapid explosive vaporization of the water content in the tissue adjacent to the electrode, which then leads to tissue fragmentation and cutting**

Although precisely how electrosurgery works is not completely understood, heat production and thermal tissue damage caused by tissue resistance to the passage of the alternating electrical current is responsible for at least the majority—if not all—of the tissue effects in electrosurgery.^{16,29,31-34} The electrical current is applied to the surgical site with a small active electrode and is collected by a large-surface return electrode that is attached to the patient's body. An active electrode can concentrate the current at a small area in its immediate vicinity and provide a sufficiently high current density to induce heating and thermal tissue damage.^{16,29} The large return electrode disperses the current, reducing the current density to levels where tissue heating is minimal.

Electrocoagulation occurs when tissue is heated below the boiling point and undergoes thermal denaturation.²⁹ An additional slow increase in temperature leads to vaporization of the water content in the coagulated tissue and tissue drying, a process called desiccation. As more superficial coagulated tissues dry out, they become less electrically conductive, potentially preventing the current from continuing to flow and heat the tissue, thereby limiting the depth of coagulation.

A sudden increase in tissue temperature above the boiling point results in rapid explosive vaporization of the water content in the tissue adjacent to the electrode. This leads to tissue fragmentation, which

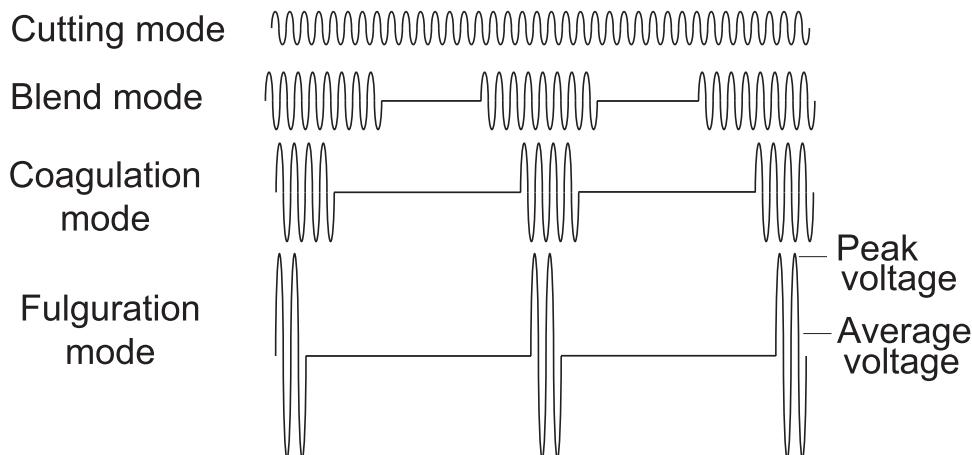


Fig 7. Different alternating electrosurgical current waveforms at equivalent output power settings. Cutting mode uses a continuous waveform that is able to provide the maximum output power of the generator. Coagulation mode uses an intermittent waveform that pulses on and off thousands of times per second. Coagulation waveform usually has a lower maximum power than cutting waveform because the delivery of the current is off for some periods of time. A coagulation waveform incorporates higher voltage than a cut waveform at the same power setting. Fulguration mode has the highest peak voltage ($\geq 10,000$ volts), which helps with large spark formation. Interrupted modes have a higher ratio of peak to average voltage than continuous mode. In previous generations of electrosurgical units, damped currents were commonly used to provide currents with high ratio of peak to average voltage. Theoretically, the surgical effects of damped currents are not different from interrupted undamped currents.

allows the electrode to pass through the tissue and is the mechanism of tissue cutting in electrosurgery (electrosection).³⁵⁻³⁷

CURRENT WAVEFORMS

Key points

- **Cutting mode uses a continuous waveform that is able to provide the maximum output power of the generator**
- **Intermittent currents have a lower maximum power and a higher ratio of peak-to-average voltage than a continuous current**
- **Fulguration mode usually has the highest peak voltage**

Electrosurgical generators are able to produce a variety of electric waveforms (Fig 7). The name of each waveform or mode does not necessarily translate to the final effect the mode has on tissue (Table I). The only variable that determines the final tissue effects of a current is the depth and the rate at which heat is produced. The waveform, voltage, and power of electrosurgical current and the size of electrode tip can affect the depth and the rate of heat production and indirectly influence the final effect of current on the tissue.^{29,38,39}

In an intermittent waveform, the voltage, amperage, and power fluctuate between 0 or

minimum in off phases and maximum in on phases. In this article, we use the term peak voltage to refer to maximum voltage of the current during on phases and the terms amperage and power to refer to the mean amperage and mean power of the current.

ELECTROSURGICAL MODALITIES

Electrocoagulation

Key points

- **Coagulation can be performed in contact mode or in spray (fulguration) mode. However, the term electrocoagulation is usually used to refer to electrocoagulation in contact mode**
- **At the end of contact electrocoagulation, the more superficial coagulated tissues may dry out (desiccation). The current may decrease or stop flowing at this time, a popping sound may be heard, and sparking may occur through the dried, nonconductive layer, leading to explosion and fragmentation of the dried layer**
- **Practically, a fine-tip electrode can be best used for superficial electrocoagulation and a large-tip electrode with a large contact area only for deep coagulation**
- **In contact mode, depth of coagulation is proportional to the size of electrode tip,**

Table II. Settings of electrosurgical units for destruction/coagulation based on the indication and type of procedure⁴⁶⁻⁵⁷

Depth of tissue injury	Size of area	Method of application of current	Electrical current or mode of choice	Alternative currents	Setting	Possible indications*
Superficial destruction with low collateral damage	Small	Fine-tip electrode and contact method	Continuous current (cutting mode)	Interrupted current (blend or coagulation modes)	Usually a very low power setting is used. The power is started very low and is increased until a reasonably fast movement of the electrode on the target can be attained. Coagulated materials can be wiped off and a second pass may be performed if necessary	Small seborrheic keratosis, freckle, lentigo, plane wart, common wart, genital wart, molluscum contagiosum, dermatosis papulosa nigra, very small skin tag, syringoma, cherry angioma, spider angioma and telangiectasia, and sebaceous hyperplasia
	Large	Fine- or large-tip electrode and fulguration [†] (spray) method	Interrupted current (fulguration mode)	Interrupted current (coagulation mode)	Depending on the speed of movement of electrode, a low to medium power setting is used. The power is started low and is increased until a reasonably fast movement of the electrode on the target can be attained. Coagulated materials can be wiped off and a second pass may be performed if necessary	Seborrheic keratosis, verrucous epidermal nevus, and rhinophyma
Medium depth destruction with some collateral damage	Small to large	Medium-tip electrode and contact method, or fine- or large-tip electrode and fulguration [†] (spray) method	Depending on the method (see above)	Interrupted currents (blend or coagulation modes)	Needs more power than superficial destruction. If curettage or shaving is performed before electrosurgery, achievement of hemostasis using electrosurgery can be (but not necessarily) an indicator of adequacy of treatment	Genital wart, [‡] rhinophyma, Bowen disease, actinic keratosis, mucous cysts, and pyogenic granuloma [§]

Deep destruction (usually used as an alternative to excision)	Medium to large	Large-tip electrode and contact method	Continuous current (cutting mode)	Medium to high power setting. The power should be enough for a slow desiccation (hearing a popping sound after a few seconds). The slower desiccation process, the deeper damage	Basal cell carcinoma, [§] keratoacanthoma, [§] and squamous cell carcinoma [§]
Loop excision	Small to large	A thin wire in loop shape	Continuous current (cutting mode)	Interrupted currents (blend or coagulation modes)	An alternative to shave excision and hemostasis; not suitable for biopsy for histopathologic evaluation; rhinophyma

*Although electrosurgery can be used for the mentioned indications, it is not necessarily the treatment of choice.
†Depending on the power and the speed of movement of the electrode on the target, electrofulguration potentially can induce either a very superficial or a relatively deep destruction.
‡Because of the risk of viral transmission through the smoke, electrofulguration is not a preferred method for the treatment of viral warts.
§Fragile tumors can be treated using curettage and electrodesiccation as an alternative to excision. However, depending on variables, such as tumor type, location, and size, for many cases of basal cell carcinoma and keratoacanthoma and most cases of squamous cell carcinoma excision rather than curettage and electrodesiccation is preferred.

power, and duration of activation time. However, a relatively low power may be able to provide a deeper maximum coagulation depth than a higher power because of delayed occurrence of desiccation with lower power

- **Fulguration mode can provide a superficial coagulation if a relatively low power is used. It can cause deeper tissue damage if a relatively higher power is used or if the activated electrode is kept over a confined area for a longer period of time**

The rate at which the tissue temperature rises is proportional to the current density in tissue. For coagulation, the current density is lower than that used for cutting to prevent tissue explosion and fragmentation. Electrocoagulation can be performed in contact mode or in spray (fulguration) mode. However, the term electrocoagulation is usually used to refer to electrocoagulation in contact mode.

For superficial coagulation of small areas (eg, the destruction of small seborrheic keratoses) a fine-tip electrode should be used to concentrate the current to a fine point (Table II). This allows the same tissue effect to be achieved with a lower power setting. When using a fine-tip electrode, the current density in tissue rapidly decreases with distance from the electrode (Fig 8); therefore, heat generation is practically confined to the vicinity of the electrode tip, potentially decreasing the depth of dermal damage and possibility of visible scar formation.²⁵

When using a large-tip electrode with a large electrode–tissue contact surface, a higher power output should be used to achieve the desired current density and tissue effect (Fig 8).⁴⁰ Current density decreases with distance from the electrode surface more slowly compared to a fine electrode. A higher power output (higher amperage) and slower decrease in current density leads to presence of a higher current density in deeper layers, resulting in deeper tissue injury. A large electrode tip (ie, ball- or disc-shaped electrodes), therefore, should be used only for deep coagulation (eg, the destruction of reticular dermis after curettage of a malignant skin tumor).⁴¹ Because superficial coagulation of large areas (eg, the destruction of large, flat seborrheic keratoses or hemostasis of oozing surfaces) using a fine-tip electrode is a slow process and takes time, spray mode coagulation or electrofulguration was developed (Table II).

In electrofulguration, the active electrode is held a few millimeters above the tissue. Using an

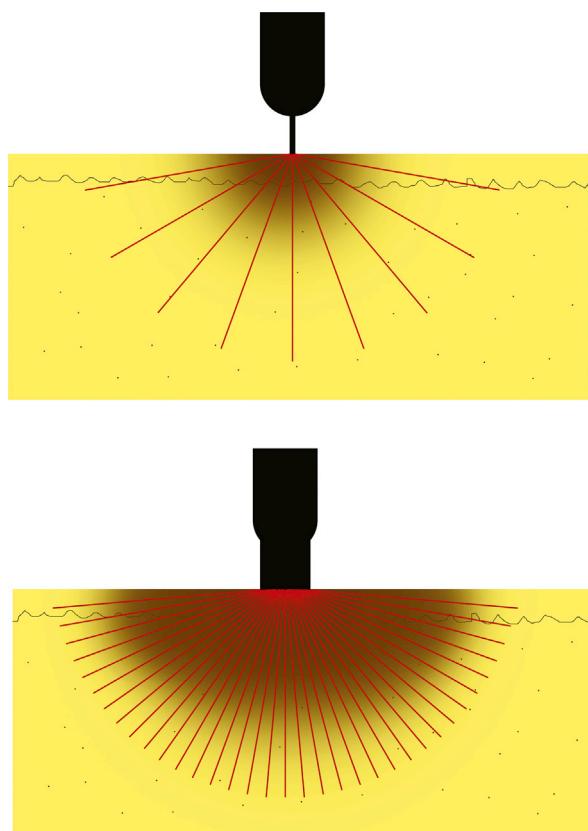


Fig 8. Electrocoagulation. A fine-tip electrode needs a low power setting and is suitable for superficial coagulation. A large-tip electrode is suitable for deep coagulation. A large electrode cannot provide a superficial coagulation because current density decreases with distance from the electrode surface slowly.

interrupted high-peaked voltage output (fulguration mode), the gap of air between the electrode and the tissue will be bridged by an electric discharge arc (spark). The arc rapidly jumps and moves from one location to the other, reestablishing itself at different locations. In this approach, the current is spread over an area larger than that of just the tip of the electrode.⁴² By moving the electrode and spraying the current over tissue, coagulation can be achieved on a large surface area faster than when operating in contact with tissue. Spray coagulation can be achieved with a fine- or large-tip electrode.

In electrofulguration, each spark carries the current to a very small point at a moment, acting as a very fine electrode. Given a relatively low power, the temperature is extremely high only at the end of each spark, leading to tissue explosion and fragmentation or charring. However, the temperature drops rapidly with increased distance from the end of the spark, and thermal damage is contained. Therefore, tissue destruction and coagulation appears within a thin superficial layer of tissue, and fulguration can be

suitable for superficial tissue destruction. However, if a fulgurating electrode is kept over a confined area, continuous heat production on the superficial layers can cause heating of deeper layers, primarily via heat conduction. In such cases, fulguration can potentially cause deep coagulation.

During electrocoagulation, the more superficial tissues may dry out. This stage of coagulation, called desiccation, is important because the current may decrease or stop flowing at this time, limiting the maximum depth of coagulation (Fig 9). When this occurs, a popping sound may be heard and/or sparking may occur through the dried nonconductive layer, leading to explosion and fragmentation of the dried layer. Desiccation is not a method or a distinctive final result—it is only a stage that may or may not happen, and it may happen at any time during the course of coagulation, regardless of the depth of the coagulated tissue. The timing of the occurrence of desiccation during the course of coagulation depends on the rate of increase in temperature that is the result of current density. With lower current density, there may be a deep coagulation before desiccation happens.²⁹ Therefore, for deep coagulation (eg, after curettage of a malignant skin tumor), a relatively low power should be chosen to provide a slow coagulation and late occurrence of desiccation. However, a very low power may not be able to provide the desired coagulation. Although there are no published data, it seems that choosing a power which can provide desiccation (popping sound) after 4 to 7 seconds can result in a relatively deep destruction. Achievement of hemostasis is not necessarily an indicator of a deep coagulation.

It seems that definitions have at times hindered a higher level of understanding of electrosurgery. The term electrodesiccation has been used in literature as a distinctive method from coagulation. Some authors use the term electrodesiccation to refer to monoterminal electrocoagulation while reserving the term electrocoagulation to refer to biterminal electrocoagulation.^{18,43,44} Others use the term electrodesiccation to refer to contact electrocoagulation as opposed to spray electrocoagulation (fulguration).^{13,45} A common and appropriate usage of the term electrodesiccation is in reference to a deep contact coagulation caused by a large electrode up to the stage of tissue drying.²⁹ This use of “electrodesiccation” is what is referred to in “electrodesiccation and curettage,” a widely used surgical technique in dermatologic surgery. Although tissue drying may also occur during fulguration, the term electrodesiccation is mainly used to refer to the final stage of contact mode coagulation.

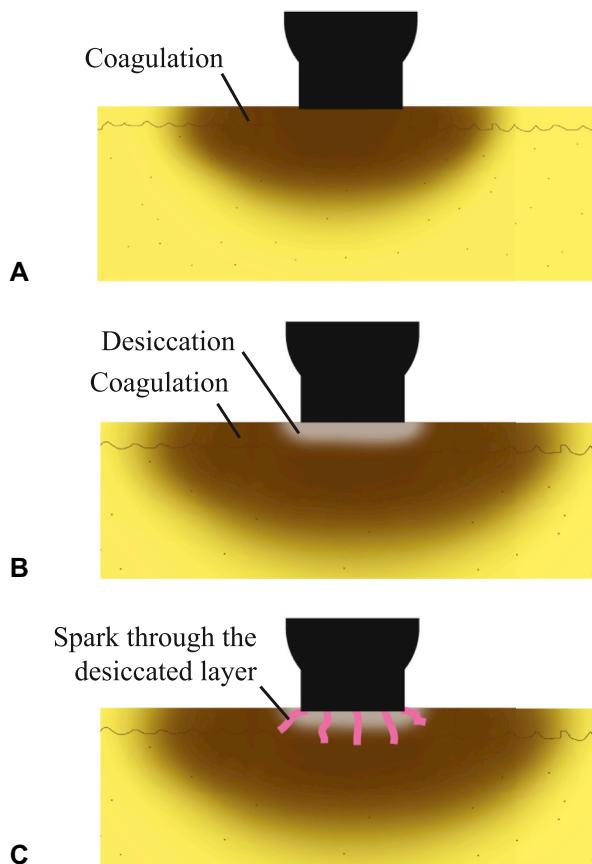


Fig 9. Electrocoagulation and electrodesiccation. The process starts with coagulation (A). At the end of coagulation, the more superficial coagulated tissue dries out (desiccation) and becomes less electrically conductive, potentially preventing the current from continuing to flow (B). However, sparking may then occur through the nonconductive desiccated layer, leading to disruption of this layer, passage of more current, more heat production, and deeper thermal damage (C).

Factors influencing the depth of coagulation

While the amount of heat generation and resulting tissue damage is proportional to the electrode–tissue contact surface area (ie, the size of the electrode tip) and the power setting (ie, waveform and voltage) used, it also depends on the duration of active contact between the active electrode and tissue. A longer activation time results in more heat generation and wider and deeper tissue damage.

One may propose that choosing a low power setting and a longer activation time is safer and produces the same result as choosing a higher power and a shorter activation time. However, this is not the case. Longer activation times result in more heat conduction and collateral tissue damage before the desired outcome is attained.^{11,40} This is similar to choosing pulse duration of lasers. Therefore, in order to minimize the collateral tissue damage (eg,

during destruction of flat seborrheic keratoses), the activation time should be short or divided into multiple pulses separated by periods of time long enough to allow the tissue to cool before the next pulse.

Electrosection

Key points

- For a pure cutting (relatively clean incision with little hemostasis) a thin electrode and a continuous cutting current (cut mode) is used. The cutting of the tissue should be brisk, using the lowest possible power setting
- A thick electrode cannot provide a pure clean cut
- Blend cutting can be performed using an interrupted current (blend or coagulation mode)

Electrosection provides a means of cutting tissue in place of a scalpel. The major advantage of this method of cutting is that hemostasis is achieved immediately upon incision by coagulation on either side of the incision wall. Larger blood vessels may still require additional spot coagulation at the completion of the cutting to achieve hemostasis.

A thin needle or wire can concentrate current on a small area in the same way that a fine-tip coagulation electrode does, and allows the same cutting effect to be achieved with a lower power setting. This leads to less heat production and less collateral tissue coagulation compared with a thicker electrode.^{37,58} Therefore, a thin needle or wire is used to make a relatively clean incision with minimal coagulation and hemostasis on either side of the incision wall (Fig 10). A thick needle electrode can cut through the tissue if a very high power current is used. In this case, current density and temperature decreases from electrode more slowly compared with a thin electrode.²⁵ The result is a deeper coagulation margin during cutting that leads to more effective hemostasis and also more tissue damage. This mode is called blend cut, meaning a blend of cutting and coagulation (Fig 10).

When the cutting electrode comes in contact with the tissue, an initial tissue heating and explosive vaporization of the medium around the electrode leads to isolation of the metallic electrode from the tissue. Ionization of the vapor around the electrode allows maintaining the current through the vapor cavity by spark. Therefore, the cutting may continue without a direct contact between the active electrode and tissue.^{25,35} The higher the peak voltage of the

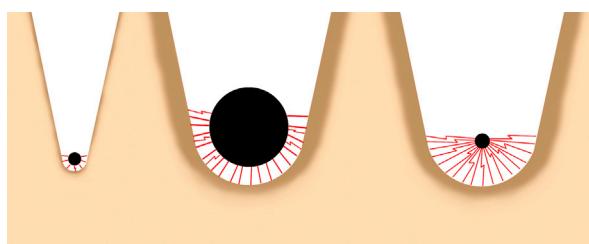


Fig 10. Cross section of tissue with 3 cutting electrodes. *Left*, A thin needle is able to concentrate a low-peaked voltage, low-power current (cutting current with relatively low power) on a small area and make a relatively clean incision with very little coagulation on the incision walls. *Middle*, A thick electrode can cut through the tissue if a higher power current is used. The result is deeper coagulation margins. *Right*, A high-peaked voltage current (blend or coagulation waveforms) produces large sparks and acts as if a thicker electrode is being used that cannot concentrate the current.

current, the larger the sparks. Larger sparks can spread current to a wider area of tissue around the electrode and act as if a thicker electrode is being used that cannot concentrate the current in a small area, resulting in a deeper coagulation (Figs 8 and 10).²⁴ Therefore, an interrupted high-peak voltage current provides deeper collateral tissue coagulation on either side of the incision walls and better hemostasis than a continuous low-peak voltage current (Figs 7 and 10).^{29,59} Blend mode or coagulation mode currents have a higher ratio of peak to average voltage than pure cut currents and can be used for making a blend cut. Depending on the technique used, the depth of coagulation on either side of an electrosurgical incision varies from 0.1 to 2 mm.⁶⁰⁻⁶² Fulguration mode currents have a very high ratio of peak to average voltage (Fig 7) and produce very thick coagulation on the incision walls if used for cutting. While there are conflicting reports of postoperative results comparing pure electrosection of the skin to scalpel surgery, electrosection, especially blend cut, is seldom used when a primary closure is planned.⁶³⁻⁶⁶

In order to have less collateral tissue damage and coagulation on the incision walls, contact time should be reduced to minimize heat production and conduction.¹¹ Therefore, the cutting of the tissue should be brisk with the lowest effective power setting.^{36,37} When the power setting is too low, the cutting process may be slow, resulting in wider collateral coagulation.³⁶ The correct output power for a clean incision can be determined by starting low and increasing the power until the maximum cutting speed can be attained. If the power is insufficient, the electrode does not glide through the tissue easily,

essentially “sticking.”³⁴ If large arcing or sparking is seen across the surface of the tissue, the voltage is too high and should be appropriately reduced. Practically, after determining the best power setting, this setting can be used for each successive patient, maybe with some fine tuning.

CONCLUSIONS

The superficial coagulation of small areas (eg, small, flat, benign epidermal tumors) can be performed with a fine-tip electrode. Cutting, blend, coagulation, or fulguration mode currents can be used; however, fulguration or coagulation mode currents are more likely to cause tissue fragmentation and deeper destruction by producing spark through the desiccated tissues. Therefore, fulguration current should be avoided for a very superficial coagulation in contact mode (contact coagulation). On the other hand, the cutting mode in some electrosurgical units cannot provide a very low power output that is necessary for a superficial coagulation using a fine-tip electrode. In this case, coagulation mode, which may have a lower minimum output power, may be used. A large-tip electrode is used for deep coagulation of a large area. A high power is usually necessary; therefore, the cutting mode may be needed. Making a relatively clean incision with little hemostasis (pure cutting) requires a thin electrode and a cutting current (cut mode). Blend cutting can be performed using an interrupted current (ie, blend or coagulation mode).

Cutting mode current is suitable for all electrosurgical methods except for fulguration, which requires a higher peak voltage. This is the reason some electrosurgical units only provide cut and fulguration modes.

A knowledgeable selection of the electrosurgical circuit, electrode configuration, power, waveform, voltage, and activation time is necessary for achieving the best possible surgical results. Surgeons should be familiar with the principles of electrosurgery and its electrophysical properties.

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Electrosurgery

Part II. Technology, applications, and safety of electrosurgical devices

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After completing this learning activity, participants should be able to compare and contrast electrosurgery with other surgical methods; describe the different technologies used in different electrosurgical units for controlling the output power, tissue effect, and patient and operator safety; and delineate the contraindications and limitations of electrosurgery.

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Electrosurgical currents can be delivered to tissue in monopolar or bipolar and monoterminal or biterminal modes, with the primary difference between these modes being their safety profiles. A monopolar electrosurgical circuit includes an active electrode and a dispersive (return) electrode, while there are 2 active electrodes in bipolar mode. In monoterminal mode, there is an active electrode, but there is no dispersive electrode connected to the patient's body and instead the earth acts as the return electrode. Biterminal mode uses a dispersive electrode connected to the patient's body, has a higher maximum power, and can be safer than monoterminal mode in certain situations. Electrosurgical units have different technologies for controlling the output power and for providing safety. A thorough understanding of these technologies helps with a better selection of the appropriate surgical generator and modes. (J Am Acad Dermatol 2014;70:607.e1-12.)

Key words: bipolar; biterminal; electrosurgery; high frequency; monopolar; monoterminal; power; radiofrequency.

INTRODUCTION

The term electrosurgery (radiofrequency surgery) refers to the passage of high-frequency electrical current through the tissue in order to achieve a specific surgical effect. Previous generations of electrosurgical generators used a spark gap and/or a vacuum tube to make the desired high-frequency electrosurgical currents. However, modern units use transistors to make high-frequency currents with a variety of waveforms. The shape of an electrosurgical current waveform does not have any direct effect on the final tissue results of the current. The only variables that determine the final tissue effects of a current are the rate and depth at which heat is produced.¹⁻³ In electrosection, the ratio of peak to average voltage of a current affects the depth of coagulation on the incision walls; with higher-peaked voltages there is deeper coagulation.^{2,4-6}

Electrosurgical currents can be delivered to the tissue in monopolar or bipolar and monoterminal or biterminal modes, with the primary difference between these modes being their safety profiles. Different electrosurgical generators may have different current waveforms, different technologies for the control of output power, and different safety technologies. A better understanding of these technologies and their applications and an awareness of potential complications of electrosurgery

helps to improve efficacy and safety of surgical procedures.

BIPOLAR VERSUS MONOPOLAR ELECTROSURGERY

Key points

- In monopolar electrosurgery, there is an active electrode and a dispersive electrode, while in bipolar mode there are 2 active electrodes
- In bipolar mode, electrical current passes only through the tissue grasped between the tips of the bipolar forceps

In electrosurgery, the prefixes mono- and bipolar refer to the number of active electrodes. In monopolar electrosurgery, an active electrode carries current to the tissue (Fig 1). Current then spreads through the body to be collected and returned to the electrosurgery unit by a large-surface dispersive electrode. The dispersive electrode is also known as the return, neutral, passive, or patient plate electrode.

Two types of dispersive electrodes are in common use today: conductive and capacitive. With the conductive type, a metallic foil or conductive polymer is attached to the patient's skin. With the capacitive type, the conductive foil has an insulating

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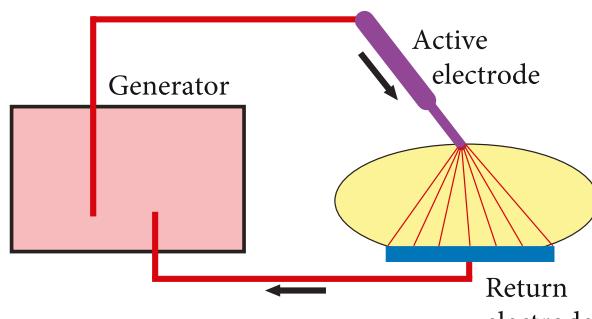


Fig 1. A monopolar, biterminal electrosurgery circuit. High-frequency electric current flows from the active electrode, through the patient's body, and then to the return (dispersive) electrode. Heat generation is practically limited to the area of high current density, meaning adjacent to the active electrode. The arrows indicate the direction of the electricity in 1 phase of current. In the next phase, the current will flow in the opposite direction. (Reprinted with permission from Taheri A, Mansoori P, Sandoval LF, Feldman SR, Pearce D, Williford PM. Electrosurgery. Part I: Basics and principles. J Am Acad Dermatol 2014;70:591-604.)

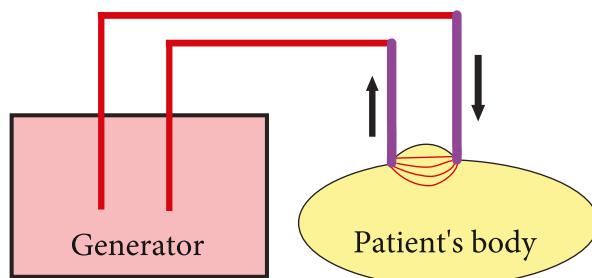


Fig 2. A bipolar electrosurgery circuit. The electric current flows from 1 forceps tine through the tissue placed between the tips to the other forceps tine, and then back to the electrosurgical generator. The bipolar mode is safer than the monopolar mode with regard to the potential extent of injury and possibility of distant site burns.

layer on the outside that prevents direct contact with the patient's skin. The insulated electrode and the patient's skin form a capacitor that passes a capacitive current.⁷ Both types of dispersive electrodes have specific advantages and disadvantages. Electrode failures and subsequent patient injury can be attributed mostly to improper application, electrode dislodgment, and electrode defects rather than electrode design.⁷

Monopolar electrosurgery should be performed with caution on an extremity such as a finger or penis because there is limited cross-sectional area for the return current to spread across. Theoretically, this may result in a higher current density and some heating throughout the volume of the extremity, leading to unintentional thermal damage if a high power is used for a relatively long activation time.

Unlike monopolar electrosurgery, where the patient's body forms a major part of the electrical circuit, in bipolar electrosurgery, only the tissue grasped between the tips of a bipolar forceps is included in the electrical circuit (Fig 2). These bipolar forceps act as 2 active electrodes.^{8,9}

The bipolar mode is used primarily for the coagulation of pedunculated benign tumors or hemostasis of blood vessels. It potentially causes less damage to surrounding tissue and reduces risk of distant site burn to the patient compared to monopolar electrosurgery.^{8,9}

BITERMINAL VERSUS MONOTERMINAL ELECTROSURGERY

Key points

- In monoterminal electrosurgery, no dispersive electrode is connected to the patient's body and the earth acts as the return electrode. Monoterminal mode can only be performed using earth-referenced electrosurgical units, which have a return electrode connected to earth
- In isolated electrosurgical units, the return electrode is not connected to earth. Therefore, there will be no current flow and no thermal effect unless the dispersive electrode is attached to the patient's body (biterminal mode)
- Biterminal mode has a higher maximum power and theoretically may be safer than monoterminal mode in certain settings
- Coagulation, fulguration, and electrosection can be performed in either biterminal or monoterminal mode; however, biterminal mode is the preferred mode for electrosection
- Inadequate contact of the dispersive electrode with the patient's body may result in a burn at this site. A contact quality monitoring system can disable the power if the dispersive electrode is not in adequate contact with patient's skin

The prefixes mono- and bi- terminal refer to the number of electrodes that are in contact with the patient's body (Figs 1 and 3). Bipolar electrosurgery is always biterminal; monopolar electrosurgery could be monoterminal or biterminal.

In so-called "earth-referenced" electrosurgical units, the return electrode is connected to earth (usually through the power supply cable), and therefore the earth and all conductive objects around the patient's body can act as a capacitive dispersive electrode (Fig 3). Electrosurgery can be performed using these units regardless of whether a dispersive electrode is attached to the patient. Performing

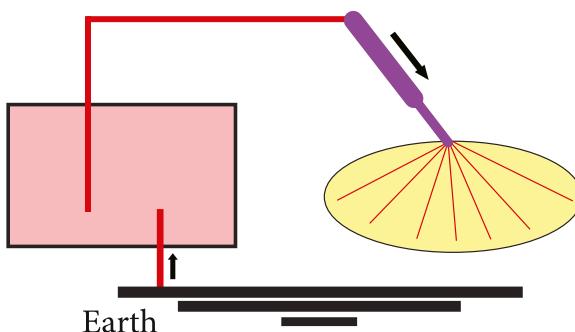


Fig 3. Monoterminal electrosurgery using an earth-referenced unit. The return electrode is connected to the earth. Therefore, the earth and all conductive objects around the patient's body can act as a capacitive return electrode. The current passes through the earth and comes back to the generator.

monopolar electrosurgery without using a dispersive electrode is called monoterminal or single-electrode electrosurgery (Fig 3). Because the maximum output power is far lower when the dispersive electrode is not used, only relatively low-powered electrosurgery can be performed in monoterminal mode.⁵ Monoterminal mode reduces the power but not the peak voltage; therefore, a pure cut cannot be performed using this mode. Biterminal is the preferred mode for electrosection.⁴⁻⁶

During monoterminal electrosurgery with an earth-referenced unit, if an electrically conductive object—such as a metal table, electrocardiogram electrode, or surgical staff—comes into contact with the patient's body, some current may select the object as a low-resistance return pathway to the ground. If the contact area is small, current concentration at this point may result in a burn at this site (Table I). For this reason, monoterminal mode can be safely used only on conscious patients who would be aware of such complications, and only on carefully insulated tables with no exposed metallic parts near the patient's body. Using a good return electrode ensures that current returns to the path of least resistance and does not take any alternative path through operators or environmental objects. Therefore, use of the return electrode, although not technically necessary for operation of an earth-referenced unit, will enhance the power and potentially safety of the electrosurgical apparatus. Earth referenced electrosurgery units are not commonly used in operating rooms today. However, many surgeons still prefer them for outpatient, office-based minor surgical procedures, avoiding the additional time and cost associated with the use of a dispersive electrode.

The type of electrosurgical unit commonly used in operating rooms today is known as floating or

isolated. In contrast to the earth-referenced units, the dispersive electrode is isolated from earth. This means that the current can return to the electrosurgery unit only via the dispersive electrode. An isolated generator will not work unless the dispersive electrode is attached to the patient—a safety feature of these units.³ During activation, if the patient's body comes in contact with an environmental object, very low or no current passes through the object and the risk of a burn is low. The surgeon can touch an active electrode and not be burned so long as he or she does not touch the patient or dispersive electrode with the other hand. Unfortunately, the isolation of these units from earth or environmental objects is never complete, because a high-frequency current is not always completely confined by insulation. Current leakage does occur by forming a capacitor between electrode cables and the floor of operating room or conductive environmental objects.^{3,4} There is still therefore a potential for distant site burns.

Although a good dispersive electrode reduces the risk of distant site burns, inadequate contact of the dispersive electrode with the patient's body may result in a smaller contact area and current concentration at this point that may lead to a burn at this site.^{1,3,18,19} Most modern electrosurgery units include a contact quality monitor for the dispersive electrode that measures the quality of the contact between the patient's skin and dispersive electrode and also between the electrode and the generator (Fig 4). If the dispersive electrode becomes dislodged or there is a high resistance between the dispersive electrode and the patient's skin, the unit will sound an alarm and the power will be disabled. Theoretically, this technology reduces the risk of burns at the dispersive electrode, but there is no clinical evidence supporting this idea.²⁰ There also have not been any clinical trials comparing the rate of side effects between an earth-referenced monoterminal device and a biterminal isolated device with or without a contact quality monitor.

The best location for placement of the dispersive electrode is a muscular site well supplied with blood vessels and adjacent to the surgical field. If there is any metal in patient's body, the dispersive pad should be placed between the metal and the surgical site to prevent current from passing selectively through the metal.

CONTROLLING THE OUTPUT POWER OF ELECTROSURGICAL DEVICES

Key points

- In constant voltage electrosurgical generators, voltage is the output variable that can

Table I. Common complications and pitfalls associated with electrosurgery^{6,10-17}

Complication and/or pitfall	Mechanism	Prevention and management
Burns	Concentration of current on the skin	When working with earth-referenced generators, using a dispersive electrode in good contact with the skin decreases the chance of burning The patient should not touch environmental conductive objects An earth-referenced generator should not be used in unconscious patients, patients with neuropathy who cannot sense the pain of a possible burn, and patients attached to an electrocardiogram or blood gas monitor
	Ignition of flammable gases	When working with isolated generators, using a dispersive electrode in good contact with the skin and a contact quality monitoring system decreases the chance of burning at the return electrode site The return electrode should be placed over an area of the skin with good perfusion (over a muscular area) and enough sensation, not on bony prominences, distal extremities, scar tissues, or foreign bodies An active electrode cable should not be put near the patient The surgeon should not touch the active electrode, even when gloved Using nonflammable cleanser before surgery and avoiding flammable anesthetic gases are mandatory. When using alcohol-based cleansers, the surface should be completely dry for a few minutes before beginning electrosurgery. Rich oxygen environments may facilitate the ignition of flammable materials and should be avoided
Cardiac arrhythmia	Modern electrosurgical currents do not stimulate cardiac tissues; however, if an internal defect were present in the generator, the low-frequency input power theoretically may be connected to the electrodes and pass through the patient body Malfunction of electronic implanted devices	If possible, the return electrode should be placed between the heart and the surgical site to prevent current from passing selectively through the heart. This theoretical complication is less likely to occur with fully isolated units An alternative method, such as scalpel surgery, electrocautery, or CO ₂ laser may be used. For electrosurgery, a return electrode should be placed between the device and the surgical site. Using bipolar mode and low power reduces the risk. If the patient is not dependent on the device, turning it off may reduce the chance of malfunction; the patient should be closely monitored
	In electrosurgery, heat is generated in tissue; therefore, the active electrode may remain cold during electrosurgery and transfer bacteria and viruses to the surgical wound Microorganisms, such as human papillomavirus, may become aerosolized in blood microdroplets or in electrosurgical smoke	Disposable or sterilized electrodes should be used An alternative method such as cryotherapy may be used; a smoke evacuator, surgical mask, and eye protection can be used; slow coagulation does not induce explosion or smoke formation and is safer than fulguration or cutting

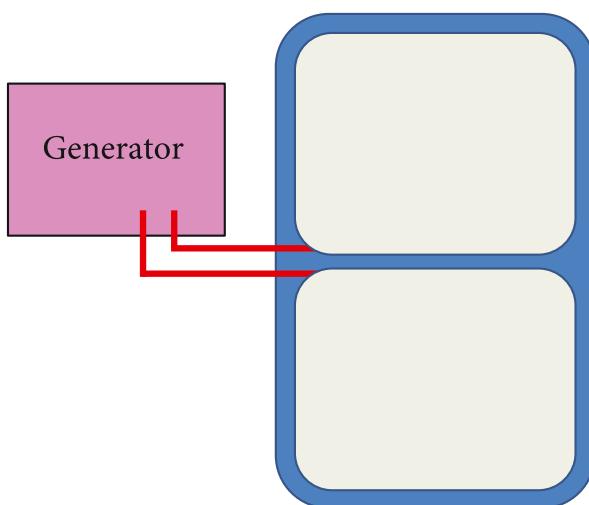


Fig 4. An electrosurgery unit with a contact quality monitor for the dispersive electrode. Contact quality is monitored by splitting the return electrode into 2 parts and measuring the resistance between the parts. If both parts are in good contact with the skin, the resistance between them will be low. If one or both parts are not in good contact with skin, the resistance will be high and the monitoring system will disable the power.

be adjusted on the display panel. The power deployed in tissue is not only dependent on this voltage but also on the resistance in the electrode–tissue contact area

- When working with a constant voltage, the quality of surgical effect is dependent on the type of tissue and its electrical resistance, but not on the size of the electrode used
- In some devices, an automatic power adjustment mode provides a constant output power regardless of tissue resistance. In this mode, the quality of surgical effect is dependent on the size of the electrode used, but not on the type of tissue or its electrical resistance, as long as the power remains constant

There are 2 types of electrosurgical generators regarding the output-power control system: constant voltage and automatic power adjustment (Fig 5).^{3,7} Most conventional electrosurgical generators use a constant voltage output system. In these generators, voltage is the output variable that can be adjusted on the display panel. The dial setting for control of voltage in these units is usually calibrated using numbers from 1 to 10. These generators deliver less power to the tissue with higher resistance compared to the tissue with lower resistance, using the same voltage setting ($W = V^2/R$; where W = power, V = voltage, and R = resistance).^{3,4,7} Therefore, working

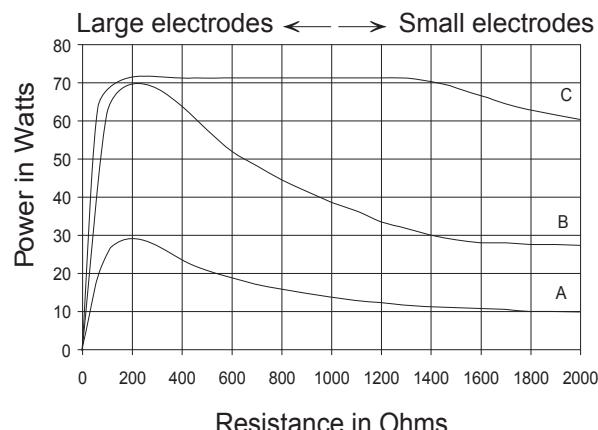


Fig 5. Power-resistance curves of an electrosurgical unit. **A**, Constant-voltage mode with a nominal load of 200 ohms, when the maximum power is set at 30 watts. **B**, The same mode when the maximum power is set at 70 watts. Increasing the size of the electrode leads to lower resistance and higher power. Therefore, current density at the electrode–tissue interface and quality of tissue effect (except for the depth of effect) will not change significantly with changing the size of electrode. However, a very large electrode–tissue contact area with <200 ohms resistance leads to a reduction in power and possibly an inability to achieve the desired surgical effect. **C**, Automatic power adjustment mode provides a constant output power between 200 and 1400 ohms. These units do not automatically adjust the power according to the electrode size.

on a dried hyperkeratotic epidermis may need a higher voltage setting than when working on the dermis to achieve the same effect.

More recent constant voltage generators are supplemented with an arbitrary dial setting with a display calibrated in watts. The indicated power refers to the maximum power that can be delivered to the nominal resistance in the circuit (Fig 5). A resistance in the circuit that is higher or lower than the nominal resistance leads to an output power lower than maximum power. Therefore, the power actually delivered to the tissue is usually lower than this maximum. This type of display has the advantage of allowing a limited degree of comparison to be made between different units or modes.

In electrosurgical generators with an automatic power adjustment system (tissue-responsive or tissue-adaptive generators), power is the output variable that can be adjusted on the display panel, with the dial setting calibrated in watts. These generators can provide a constant power in a wide range of resistances in the circuit (Fig 5, C). They can provide the same surgical effect in different tissues with different electrical resistances at the same

Table II. The choice of the electrosurgical unit based on the surgical setting

Setting and indications	Commonly used devices	Advantages	Disadvantages
Major surgeries and endoscopic (urologic) procedures in operating rooms	High power (usually 200–400 watts), isolated generators, with constant-voltage or automatic power adjustment mode	More available modes and flexibilities	Expensive; some devices may lack an ability to provide a very low output power for very superficial minor destructions
Minor dermatologic procedures on conscious patients	Low power (usually around 40–100 watts), earth-referenced units, with constant-voltage output mode	More cost-effective and convenient to use	Lower safety profile; may have fewer available modes and flexibilities; some have only 1 interrupted current for coagulation and fulguration
Most dermatologic procedures	Low power (usually around 70–200 watts), isolated units, with constant-voltage output mode	Safest profile	May be less convenient to use than earth-referenced units

Note: Some electrosurgical units show an index named "crest factor" that is the ratio of peak voltage to average voltage of their continuous cutting current. Generators with lower crest factors are able to provide cleaner cuts with less collateral damage and less hemostasis in pure cutting mode. Most available electrosurgical units in the market have an output frequency of 0.3–5 MHz. There is no strong evidence showing any relation between frequency of electrosurgical currents and their effects on tissue. A few studies are available but can be criticized because of poor study methods.²¹

power setting.^{3,7} However, if the electrode–tissue contact area is increased, power is not increased in proportion with the contact area. Therefore, the power setting should be increased manually to provide enough power to warm up a larger area and create the same surgical effect. Both technologies have specific advantages and disadvantages. The choice of one technology may depend on the surgeon's preferences and the price of the unit (Table II).

CLINICAL CONSIDERATIONS IN ELECTROSURGERY

Key points

- **Electrosection results in the histologic distortion of surgical margins.** For specimens requiring histopathologic analysis, scalpel surgery is preferred
- **Hemostasis of a bleeding vessel can be performed by clamping the vessel and passing a relatively low-power continuous current (cutting mode) through the clamp.** Current flow should be stopped when a popping sound is heard or spark is seen
- For hemostasis of an oozing surface, contact coagulation is the preferred mode. Fulguration usually is less efficient because it results in fragmentation of the coagulated layer
- Penetrating proximally insulated electrosurgical electrodes can be used for coagulation of subcutaneous targets, such as tumors or varicose veins
- Fractional radiofrequency skin rejuvenation devices which use penetrating electrodes are used for fractional heating of the dermis and collagen remolding while preserving the epidermis

Electrosection versus scalpel surgery

Electrosection results in more collateral tissue damage compared to scalpel surgery, creating some histologic distortion of surgical margins. Thermal damage causes carbonization at the excision margin, vessel thrombosis, and collagen denaturation.^{22,23} Cellular changes may include vacuolar degeneration, shrunken and shriveled cell outlines with condensation and elongation of the nuclei, or fusion of cells into a structureless homogeneous mass with a hyalinized appearance.²⁴ In frozen sections, normal structures may mimic tumors, such as basal cell carcinoma.²⁵ It also may make it impossible to distinguish squamous and melanocytic neoplasms. For specimens requiring histopathologic analysis—especially during the excision of tumors

that require the margins to be assessed—scalpel surgery is preferred. Electrosection in pure cutting mode may cause less thermal damage artifact than using a blend cut.^{26,27}

Electrosection often serves as an alternative to scalpel surgery; however, there is conflicting evidence in studies comparing these modalities with respect to outcomes, such as postoperative pain, infection, wound healing, and scar formation. While many studies support better outcomes using scalpel surgery, there is also literature favoring electrosection.^{26,28-30} A general concept is to avoid electrosection for cutting skin when a primary closure is planned.

Electrosection versus CO₂ laser surgery

Like electrosection, CO₂ laser can provide coagulation of the incision walls and hemostasis. Both techniques, especially electrosection, are operator-dependent and cannot be standardized. Therefore, it is not easy to compare these methods in clinical settings. There is conflicting evidence in studies comparing the depth of collateral injury and final results of surgery using these modalities. While some studies show more collateral coagulation using a CO₂ laser, others report the opposite results.^{27,29-36} Compared to CO₂ lasers, electrosurgery generally is less expensive, does not require eye protection, and is more accessible.

Electrocoagulation for achieving hemostasis

Hemostasis of a bleeding vessel can be performed by clamping the vessel and passing a monopolar current through the clamp or using a bipolar electrode.³⁷ Care should be taken to prevent spark formation and tissue fragmentation or charring at the end of coagulation. A relatively low-power continuous current (cutting mode) is the preferred current in order to prevent large spark formation. A popping sound may be heard or a spark may be seen at the time of desiccation, and at this time current flow should be stopped.⁵ For hemostasis of an oozing surface, contact coagulation is the preferred mode. Fulguration usually is less efficient because it results in fragmentation of the coagulated layer. Wiping of the coagulated area should be avoided if possible, because it can cause disruption of the coagulated layer and result in more bleeding. One should remember that coagulation of a surface for achieving hemostasis results in damage to the surface that may adversely affect postoperative and aesthetic outcomes.^{4-6,38}

To optimize hemostasis, the operative field should be dry, because blood diffuses the current flowing from the electrode. A dry operative field is also essential for cutting and coagulation. Proximally insulated bipolar electrodes can help with more

effective hemostasis in wet environments. Electrocautery, as opposed to high-frequency electrosurgery, may function in wet environments, although not as effectively as in dry fields.

Electrosurgery for hair removal

Hair removal can be performed using a needle electrode that enters the hair follicle and applies a direct electrical current (galvanic current). The resulting chemical reaction (electrolysis) around the electrode destroys the hair follicle. The process is relatively slow and time-consuming. Using an electrosurgical alternating current, the follicle can be destroyed using thermal damage (thermolysis). This process is faster than electrolysis; however, there is a greater risk of damage to the dermis around the hair follicle and scar formation.³⁹⁻⁴¹

Electrosurgery in the treatment of malignant skin tumors

Curettage and electrodesiccation has been used successfully in the treatment of many different benign and malignant skin tumors.⁴²⁻⁴⁴ For treatment of cancers, this procedure is usually repeated ≥ 2 times in an attempt to remove any small tumor extensions. The procedure may be less morbid, faster, and more cost-effective to perform than excision and repair in certain cases with certain tumors. A great advantage of curettage over surgical excision arises from the ability of a semisharp curette to differentiate and remove friable abnormal tissue from the normal surrounding tissue with minimal sacrifice of normal skin.⁴⁴ However, this method is operator-dependent and cannot be easily standardized because the depth of coagulation achieved is dependent on many factors, such as size of the electrode and power used.⁴⁵ Treatment of basal cell carcinoma with curettage and electrodesiccation results in cure rates ranging from 88% to 99% depending on the location and size of tumor and the surgical method used. Studies that reported the highest cure rates destroyed a wider peripheral margin around the initial curettage, ranging from 2 to 8 mm.^{6,46-50}

Electrosurgery in the treatment of benign superficial skin tumors

Upon a mild thermal coagulation, the epidermis and papillary dermis turns to a soft material (liquefaction) that can be easily wiped off of the surface of the skin surface. However, the reticular dermis does not respond in the same way; instead, it maintains its durability and remains solid and cannot be wiped off after coagulation or desiccation.⁵¹ This phenomenon

helps the surgeon to distinguish the papillary from the reticular dermis.

For the treatment of superficial epidermal overgrowths, such as seborrheic keratoses or plane warts, a very superficial coagulation using a fine-tip electrode or electrofulguration with a low output power can be performed. The area may be wiped off after coagulation to see if any epidermal tissue remains in place that requires a second pass of superficial coagulation.

To achieve a very superficial coagulation using a fine-tip electrode, a very low power should be chosen. Spark formation that occurs at the time of desiccation indicates the occurrence of deeper injury and should be avoided by reducing voltage, power, and/or contact time.

Penetrating insulated electrosurgical electrode for the destruction of subcutaneous targets

Electrocoagulation of a variety of tumors in internal organs has been performed using penetrating, proximally insulated electrodes.^{52,53} Recently, this approach has been used for the treatment of the deeper component of infantile hemangioma of the skin.⁵⁴

Endovascular thermal ablation of varicose veins using a long, flexible electrosurgical electrode with insulation on the proximal parts is used as a less invasive alternative to traditional surgery.^{55,56} Compared to surgery, this approach provides the same efficacy with less postoperative morbidity and a lower rate of adverse events.⁵⁷ Proximally insulated needles can also be used for treating telangiectasias.⁵⁸

Penetrating insulated electrodes have also been used for ablation or denervation of corrugator supercilii muscle for treatment of hyperdynamic vertical glabellar furrows.⁵⁹⁻⁶¹

Electrosurgical currents in aesthetic medicine and skin rejuvenation

High-frequency electrical currents (radiofrequency technology) has been used for the treatment of cellulite, acne scar, inflammatory acne, skin resurfacing, and nonablative tightening of skin to improve laxity and reduce wrinkles.⁶²⁻⁷⁰ Most of the devices marketed for these purposes use ≥ 1 electrodes to deliver the current to the skin surface (epidermis). However, the manner in which some of these devices work is not completely understood.⁷¹ For skin tightening, the most acceptable explanation is that the heating of dermal tissue by high-frequency (radiofrequency) currents results in remodeling of collagen fibers and subsequent neocollagenesis.^{66,72} Most of these methods have struggled to gain attention in the

scientific literature, and there is a paucity of well-conducted randomized trials supporting their efficacy.⁷² There is evidence, however, of the success of fractional radiofrequency systems with penetrating electrodes in dermal heating and collagen remodeling. In contrast with the devices that deliver the current to the epidermis, these devices deploy energy directly to the dermis.⁷³⁻⁷⁷ Multielectrode pins of these devices provide heating of the areas that are directly targeted by the electrodes, leaving intact or only slightly affected zones between the targeted areas.⁷³⁻⁷⁷ The preserved tissue serves as a pool of cells that promote rapid wound healing.

Depending on the technology used, when an electrode of a fractional radiofrequency device enters the skin, the maximum heating effect can be around the tip of the electrode in dermis because high-frequency electrical currents have a tendency to propagate toward the center of the bulk of tissue.⁷⁸ This phenomenon can preserve the epidermis during dermal heating and reduce the risk of postprocedural side effects, including postinflammatory dyspigmentation. By insulating the proximal end of the penetrating electrode, the epidermis will escape injury more efficiently during heating of the dermis.⁷⁹ In contrast to radiofrequency currents, laser-based fractional resurfacing may produce greater tissue injury on the surface of the skin (epidermis) than in the reticular dermis.^{80,81} However, to our knowledge there is no clinical trial comparing these modalities.

Electrosurgery and implantable electronic devices

Electrosurgery has been reported to cause destruction, reprogramming, depleted battery, and inhibition or activation of implantable electronic devices. Skipped beats, asystole, bradycardia, ventricular fibrillation, and unspecified tachyarrhythmia have been reported with use of electrosurgery in patients with cardiac implantable electronic devices.⁸²⁻⁸⁴ The incidence of interference is higher when using the monopolar rather than bipolar mode, using a higher power, working near the implanted device, or having the pacemaker between the active and dispersive electrode.⁸² Recent improvements in electrical shielding and filtering systems have made implanted electronic devices more resistant to outside electrical interference.⁸⁴ Heat electrocautery is a safe alternative to electrosurgery in patients with implanted electronic devices.

Practical differences between different electrosurgical units

Electrosurgical units have different output power, output frequency, and can provide different modes.

The choice of the unit depends on the surgical setting and the desired applications (Table II).

CONCLUSIONS

Bipolar electrosurgery is primarily used for the coagulation and hemostasis of small- to medium-sized blood vessels or in certain situations, such as surgery on a finger or a patient with an implantable electronic device. The bipolar mode theoretically can be safer than the monopolar mode with regard to the potential extent of injury and possibility of distant site burns.

With regard to safety, the monoterminal mode may be limited in electrosurgery, especially when using a high power on an unconscious patient or a patient with neuropathy who cannot sense the pain of possible burns. However, if an earth-referenced device cannot provide a very low power for a fine coagulation, the monoterminal mode can be used to reduce output power. The correct use of a return electrode increases the power and safety of the electrosurgical device.

Although the application of electricity in surgery dates back 100 years, progress in technology still leads to the introduction of new methods and indications. More recent applications of electrosurgery include the treatment of varicose veins, treatment of benign subcutaneous tumors, and fractional skin rejuvenation. A thorough understanding of the technology and its possible complications can promote effective application of electrosurgical techniques and improved outcomes.

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The spectrum of oculocutaneous disease

Part I. Infectious, inflammatory, and genetic causes of oculocutaneous disease

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Learning Objectives

After completing this learning activity, participants should be able to recognize infectious, inflammatory, and genetic oculocutaneous diseases; recognize and differentiate the cutaneous manifestations of several ocular disorders; describe the pathophysiology and genetics of how ocular disorders may manifest cutaneously; and order appropriate tasks and initiate timely referral to ophthalmologists and other subspecialists for early diagnosis, surveillance, and treatment of ocular disease.

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Many skin diseases are associated with ocular findings, emphasizing the need for dermatologists to be fully aware of their presence, and as a result, avoid overlooking conditions with potentially major ocular complications, including blindness. We review important oculocutaneous disease associations with recommendations for the management of the ocular complications and appropriate referral to our ophthalmology colleagues. Part I of this 2-part review focuses on the infectious, inflammatory, and genetic relationships. (J Am Acad Dermatol 2014;70:795.e1-25.)

Key words: autoimmune; dermatology; genetic; infection; inflammatory; oculocutaneous; ophthalmology.

INTRODUCTION

Currently, there is no comprehensive review of the association between cutaneous dermatoses and ocular disease in the dermatologic literature. We review important oculocutaneous disease associations with recommendations for the diagnosis, management, and appropriate referral to our ophthalmology colleagues. This review is divided into 2 parts: part I focuses on the infectious, inflammatory, and genetic relationships of oculocutaneous diseases, and part II addresses neoplastic and drug-related oculocutaneous conditions. A glossary of ophthalmology terms (Table I) and review of ocular anatomy (Fig 1) have been included.

INFECTION

A summary of eye findings in infectious oculocutaneous diseases and recommendations regarding when to refer to ophthalmology if a patient has signs/symptoms of ocular disease can be found in Table II.

Viral

Herpes simplex virus

Key points

- Ocular herpes simplex virus is a leading cause of blindness in developed countries and worldwide

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- The acute “dendritic ulcer” of ocular herpes simplex virus may progress to chronic scarring keratitis and visual impairment
- Intraocular topical antiviral medications, corticosteroids, and debridement help prevent scarring, and systemic antiviral therapy decreases the risk of recurrence

Ocular herpes simplex virus (HSV) has a reported annual incidence of 20.7 cases (new and recurrent) per 100,000 people per year and is the most common cause of corneal blindness in developed countries and unilateral corneal blindness worldwide.¹ Ocular HSV typically presents with grouped, painful vesicles near or around the eye. In addition, it can cause conjunctivitis or blepharoconjunctivitis, in which vesicles are seen on the eyelid. There are 2 important ocular complications of HSV: epithelial and stromal keratitis. Epithelial keratitis presents with a characteristic “dendritic ulcer,” caused by inflammation of the epithelial surface of the cornea. Stromal keratitis, seen more commonly with recurrent HSV infection, is caused by inflammation of the middle corneal layer with the potential to cause corneal scarring and future blindness.^{2,3} Early diagnosis and treatment are imperative to prevent these complications. Patients with grouped

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Table I. Glossary

Blepharitis	—inflammation of the eyelid seen with meibomian gland dysfunction and seborrheic blepharitis. Staphylococcal blepharitis is infectious; usually associated with <i>Staphylococcus aureus</i>
Chalazion	—granulomatous inflammation of a meibomian gland or gland of Zeis
Dacryocystitis	—inflammation of the lacrimal sac caused by blockage of nasolacrimal duct
Hordeola, external (sty)	—acute infection of the glands of Moll or Zeis
Hordeola, internal	—acute infection of a meibomian gland
Hypopyon	—pus or inflammatory cells layered in the anterior chamber
Keratoconus	—cone-shaped deformity of the cornea
Keratitis	—inflammation or microbial infiltration of the cornea
Lagophthalmos	—incomplete eyelid closure with environmental exposure
Madarosis	—missing eyelashes
Nystagmus	—an involuntary rhythmic oscillation of the eyeball that may be horizontal, vertical, torsional, or mixed
Optic neuritis	—inflammation of the optic nerve that carries visual impulses from the retina to the brain
Scleritis	—inflammation of the tough white outer covering of the eye, the sclera, that, with the cornea, forms the external protective coat of the eye. Caused by immune-mediated vasculitis that leads to destruction of the sclera
Strabismus	—misalignment of the eyes
Symblepharon	—adhesions between the bulbar and palpebral conjunctiva
Uveitis	—inflammation of one or all portions of the uveal tract (ie, iris, ciliary body, and choroid)

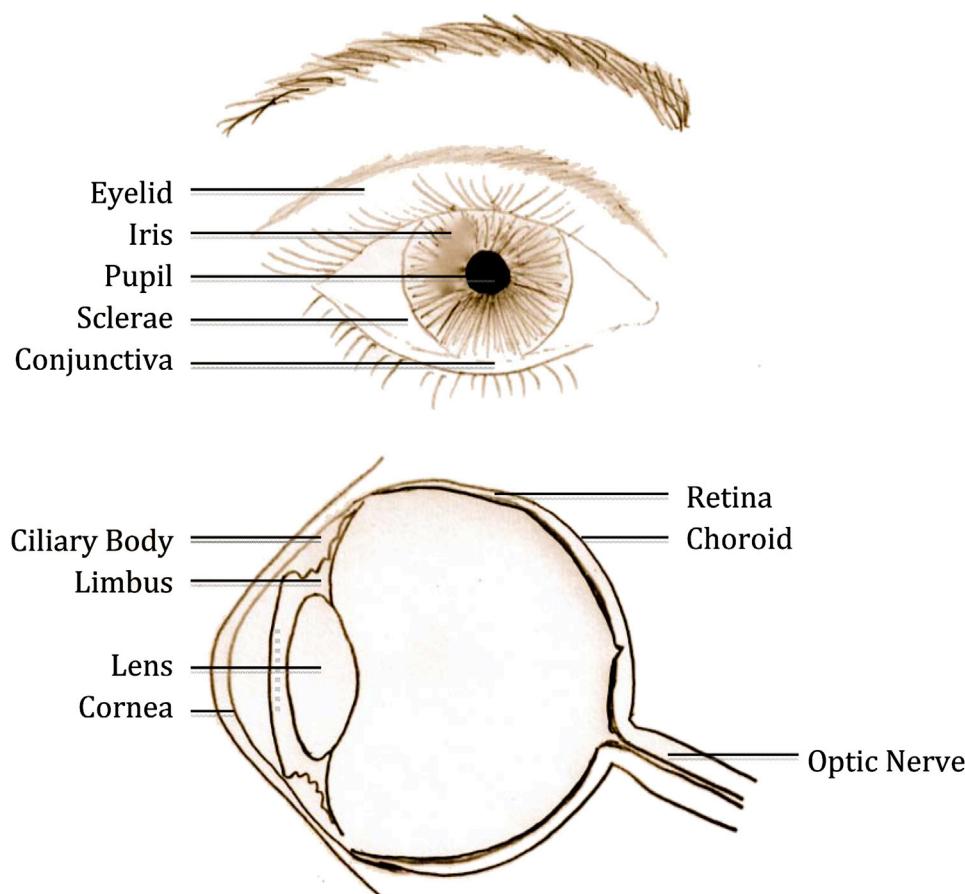


Fig 1. Anatomy of the eye.

vesicles near the eye should be immediately referred to the ophthalmology department, where ocular HSV is diagnosed with fluorescein stains and a slit lamp examination.²

Therapy. Ophthalmologists treat ocular HSV promptly with antiviral medications, corticosteroid eye drops, and debridement (when indicated).¹ The Herpetic Eye Disease Study (HEDS) compared

Table II. Summary of eye findings in infectious oculocutaneous diseases and recommendations on when to refer to an ophthalmologist if a patient has signs/symptoms of ocular disease

Infection	Ocular manifestations	Referral time*
Viral		
Herpes simplex	Dendritic ulcer, stromal keratitis, and retinitis	Urgent
Herpes zoster	Conjunctivitis, stromal keratitis, neurotrophic keratitis, and retinitis	Urgent
Molluscum	Chronic conjunctivitis	Nonurgent
Bacterial		
Cat-scratch disease	Unilateral conjunctivitis with lymphadenopathy	Urgent
Reactive arthritis	Bilateral mucopurulent conjunctivitis	Nonurgent
Syphilis	Uveitis (secondary) and Argyll–Robertson pupil (tertiary)	Urgent
Lyme disease	Uveitis	Nonurgent
Periorbital cellulitis	Erythema, induration, tenderness, and/or warmth	Not necessary
Orbital cellulitis	Periorbital findings and proptosis and/or limited ocular motility	Immediate
Mycobacterial		
Tuberculosis	Variable granulomatous intraocular diseases	Nonurgent
Leprosy	Keratitis from chronic environmental exposure	Nonurgent
Parasitic		
Onchocerciasis	Edema and injection causing scarring keratitis	Urgent
Schistosomiasis	Uveitis and subretinal granulomas	Urgent

*Immediate: same day as presentation; urgent: same week as presentation; nonurgent: when available.

placebo with corticosteroid drops in addition to antiviral eye drops (trifluridine) and found a 68% reduction in the progression of stromal inflammation and a shorter overall duration of HSV stromal keratitis.⁴ Daily oral antiviral medications (ie, acyclovir or valacyclovir) reduce the risk of ocular HSV recurrence by 50%, but this effect is negated once the medication is discontinued.² These patients should be closely followed by the dermatology and ophthalmology departments jointly to ensure optimal treatment outcomes.⁵

Herpes zoster

Key points

- One in 6 herpes zoster cases will affect the V₁ nerve distribution, and more than half of these cases will suffer visual sequelae
- The Hutchinson sign is 85% specific and 50% sensitive for ocular herpes zoster

The lifetime risk of herpes zoster in the United States ranges from 20% to 30%, with a predilection for affecting both elderly and immunosuppressed individuals.⁶ Zoster ophthalmicus, or herpes zoster of the nasociliary branch of the trigeminal nerve (V₁; Fig 2), accounts for 15% of all zoster cases. Between 50% and 70% of zoster ophthalmicus cases have subsequent visual defects.^{6,7} Herpes zoster damages the eye via 3 mechanisms: (1) direct viral invasion, causing superficial keratitis and conjunctivitis, (2) secondary inflammation, leading to stromal keratitis, uveitis, scleritis, choroiditis, occlusive retinal vasculitis, retrobulbar optic neuritis, episcleritis, and cranial nerve palsies; and (3) neurotrophic



Fig 2. Herpes zoster. Note the vesicles on an erythematous base affecting the V₁ distribution.

changes resulting in neurotrophic keratitis. The latter 2 mechanisms are responsible for the irreversible sequelae of herpes zoster ophthalmicus.⁷

Clinically, patients have vesicles and erythema in the trigeminal nerve distribution. Patients may report eye pain, pressure, or blurred vision. The Hutchinson sign (vesicle on the tip of the nose) is highly predictive (up to 85% specific, but only 50% sensitive) for intraocular involvement.⁶ Serologic antibodies and viral cultures can be confirmatory,

but the diagnosis of trigeminal zoster is usually made clinically.⁶

Therapy. Immediate ophthalmologic referral is essential in patients with suspected trigeminal zoster to prevent permanent visual impairment.⁸ Early treatment (within 72 hours of symptom onset) with either oral acyclovir 800 mg 5 times daily or valacyclovir 1000 mg 3 times daily for 7 days not only helps prevent ocular complications but also minimizes the acute pain and postherpetic neuralgia.^{7,9}

Molluscum contagiosum

Key point

- When molluscum contagiosum lesions are located close to the conjunctiva or interfere with vision, patients may require referral to the ophthalmology department for treatment

Ocular molluscum contagiosum is rare among immunocompetent individuals, but it has an increased incidence in patients with HIV (5-10%)^{10,11} and with pediatric atopic dermatitis (18%).¹²

Ocular molluscum presents with several small umbilicated papules on the eyelid that can be associated with chronic follicular conjunctivitis because of hypersensitivity or toxicity from the viral proteins shed by the eyelid papules (Fig 3).¹³ Patients with HIV-associated molluscum have persistent, larger lesions (up to 5 mm in diameter), and patients with atopic dermatitis have an increased number of lesions (up to several hundred).^{13,14}

Therapy. Lesions located very close to the conjunctiva, interfering with vision, or associated with conjunctivitis require ophthalmologic referral for surgical removal (ie, controlled cryotherapy, unroofing and curettage, or excision).^{10,13,15} If the molluscum lesions are not contiguous with the conjunctiva, immunocompetent patients may choose observation over treatment, and the lesions usually resolve spontaneously in 6 to 24 months, similar to their course on the skin. In patients with HIV, clearance of molluscum typically occurs after 5 to 6 months of antiretroviral therapy.^{10,11}

Bacterial

Cat-scratch disease (*Bartonella benselae*)

Key points

- Parinaud oculoglandular syndrome is characterized by unilateral conjunctivitis with regional lymphadenopathy, which can progress to optic nerve swelling and decreased vision
- Urgent ophthalmology referral is indicated with any suspected eye involvement

B benselae is a Gram-negative bacillus transmitted to humans via the cat flea (*Ctenocephalides felis*)



Fig 3. Molluscum contagiosum affecting the right upper eyelid in a young child. (Photograph courtesy of Fred Ghali, MD.)

through a cat scratch or bite. Infection begins with fever, malaise, and an erythematous papule at the site of inoculation with associated regional lymphadenopathy. Ocular involvement typically follows systemic symptoms. The most common ocular manifestation of cat-scratch disease is Parinaud oculoglandular syndrome (POS), or unilateral granulomatous conjunctivitis with regional lymphadenopathy. Patients experience a unilateral decrease in visual acuity, unilateral conjunctival injection, and a foreign body sensation. Bartonella can also lead to neuroretinitis (inflammation of the optic disc) and optic neuritis.¹⁶

Clinical suspicion can be confirmed with polymerase chain reaction (PCR) studies for anti-*B benselae* antibodies, which is 62% sensitive and 100% specific.^{15,16}

Therapy. Patients with any visual symptoms—especially those with any evidence of decreasing visual acuity, conjunctivitis, and unilateral lymphadenopathy—need to be referred urgently to an ophthalmologist. Treatment of primary cat-scratch disease consists of oral rifampin, tetracycline, ciprofloxacin, or trimethoprim-sulfamethoxazole.¹⁷ Azithromycin and erythromycin have also been used successfully.

Reactive arthritis (formerly Reiter syndrome)

Key points

- Reactive arthritis is predominately caused by *Chlamydia trachomatis*, but may also be triggered by other infectious agents
- Conjunctivitis may be recurrent and chronic, requiring ophthalmology monitoring and treatment

Reactive arthritis involves acute oligoarthritis (especially of the knee and ankle), urethritis, and conjunctivitis shortly after infection by a sexually transmitted disease (*C trachomatis*), gastroenteritis (Salmonella or *Campylobacter* species), HIV, or even HSV or cytomegalovirus.^{15,18} Clinical manifestations include: circinate balanitis, keratoderma blennorrhagicum,

psoriasiform skin lesions, dactylitis, cervicitis, onychodystrophy, and mouth ulcers.¹⁵ Human leukocyte antigen-B27⁺ patients are at increased risk.¹⁵

Ocular findings occur in 58% of patients with reactive arthritis and are most commonly associated with chlamydial etiology.¹⁵ Within a few weeks of onset of urethritis and arthritis, patients develop bilateral, mucopurulent papillary conjunctivitis. Eye findings of episcleritis, iridocyclitis, and keratitis can also be seen. Patients frequently experience bilateral eye pain and photophobia, which usually resolve without treatment in 10 days. Up to 12% of patients with conjunctivitis develop an anterior uveitis associated with recurrent episodes of inflammation and long-term visual sequelae.¹⁹

The diagnosis of reactive arthritis is clinical, but can be confirmed by conjunctival, cervical, and/or urethral culture, and is supported by elevated leukocyte counts, erythrocyte sedimentation rates, and C-reactive protein levels.¹⁵

Therapy. The conjunctivitis and arthritis typically resolve spontaneously in weeks to months. However, any ocular involvement beyond the initial conjunctivitis warrants ophthalmology referral for stepwise treatment with oral nonsteroidal antiinflammatory drugs, oral/topical corticosteroids, and immunosuppressive therapy to preserve vision.¹⁸⁻²⁰ If an underlying infection is present, the appropriate antimicrobial treatment is also required.

Syphilis (*Treponema pallidum*)

Key points

- Ten percent of secondary syphilis cases involve the eyes
- The Argyll–Robertson pupil of tertiary syphilis is caused by papillary constriction for accommodation, but not in response to light
- Ocular complications of congenital syphilis can occur between 5 and 20 years of age

The eyes are affected in 10% of secondary syphilis cases.²¹ However, the diagnosis of ocular syphilis is frequently delayed, because it may mimic many different eye disorders—as it does in the skin.²¹ While the primary chancre may affect the eyelid or conjunctiva, the most common finding is uveitis, frequently seen as early as 6 weeks after primary infection (Fig 4).²¹ Secondary syphilis can cause uveitis, optic neuritis, retinitis, conjunctivitis, dacryocystitis, dacryoadenitis, scleritis, or interstitial keratitis. Patients may complain of eye pain, photophobia, and decreased visual acuity. Blurred vision is also common in tertiary neurosyphilis, including the pathognomonic Argyll–Robertson pupil of light-near dissociation, in which pupils constrict with accommodation but do not react to direct light.^{22,23}



Fig 4. Syphilis. Fluorescein angiogram revealing optic nerve inflammation in a patient with syphilitic uveitis. (Photograph courtesy of Robert Wang, MD.)

Despite prenatal screening efforts, congenital syphilis rates increased from 8.2 to 10.1 per 100,000 live births in the United States between 2003 and 2008.²⁴ While half of the neonates born with congenital syphilis are asymptomatic, up to 40% develop a blistering eruption by 2 years of age, emphasizing the need for dermatologists to consider syphilis. Many will have low birth weight (10-40%), hepatomegaly (33-100%), bone changes on radiography (75-100%), respiratory distress (57%), bleeding (10%), pseudoparalysis (36%), and fever (10%) in addition to the classic clinical findings of Hutchinson teeth, saddle nose deformity, and deafness.²⁵ Ocular complications of interstitial keratitis, such as conjunctival injection, an irregular pupil, photophobia, and eye pain, can present between 5 and 20 years of age.²⁶

Darkfield microscopy of clear eye secretions may identify an organism, but serum rapid plasma reagin/Venereal Disease Research Laboratory and fluorescent treponemal antibody absorption testing is more commonly performed.¹⁵

Therapy. The Centers for Disease Control and Prevention recommend that all patients with ocular manifestations of syphilis have their cerebrospinal fluid evaluated for neurosyphilis. In addition to treating the treponemal infection, referral to the ophthalmology department is appropriate because patients may require adjunct therapy with topical, periocular, and systemic corticosteroids.²¹ Parenteral penicillin G is the preferred treatment for all stages of syphilis and should be initiated immediately upon diagnosis.

Lyme disease (*Borrelia burgdorferi*)

Key points

- Mild conjunctivitis is the most common eye finding of Lyme disease, occurring in 10% of patients during the early stage of infection
- Lyme disease can affect the eye during any stage and lead to blindness

Lyme disease is a potentially devastating infection transmitted by the *Ixodes scapularis* tick, which is endemic in Connecticut, New York, Minnesota, and Wisconsin, but can be seen throughout the United States and worldwide.^{22,27} After a tick bite, the incubation period lasts up to 30 days. Thereafter, patients develop the characteristic skin manifestations of erythema chronicum migrans, fever, malaise, and arthralgia.²² The spirochete invades the eye early in the course of Lyme disease and causes a variety of sequelae at each stage.²⁸ Mild conjunctivitis is the most common ocular finding (seen in 10% of cases), but a wide range of ocular findings have been reported, including photophobia, periorbital edema, keratitis, optic neuritis, optic atrophy, papilledema, and papillary abnormalities.²⁹

In addition, neuroophthalmic disorders, such as cranial nerve VI palsy and paralytic mydriasis, have been reported and cause visual disturbances.³⁰ Photophobia or ocular pain in a patient with possible Lyme disease warrants ophthalmology referral.²⁷

The Centers for Disease Control and Prevention recommend initial screening of serum with an enzyme immunoassay and then performing a Western blot assay for Lyme confirmation.^{22,27}

Therapy. Treatment of early-stage Lyme disease is oral doxycycline (100 mg twice daily for 14–21 days). Late-stage disease requires ceftriaxone (2 g intravenously daily for 14 days).¹⁵ Doxycycline (200 mg orally) can prevent Lyme disease if given within 72 hours of a tick bite.^{22,27} Topical steroid eye drops and mydriatic medications help inflammatory eye changes. The majority of cases of ocular damage will resolve within a year after antibiotic therapy. However, patients with retinal damage can develop permanent visual sequelae.²²

Periorbital and orbital cellulitis

Key points

- It is important to distinguish periorbital (or preseptal) cellulitis from orbital (postseptal) cellulitis, because the latter may potentially cause a life-threatening infection via direct extension into the brain
- Orbital cellulitis characteristically has associated proptosis and limited ocular motility

Orbital cellulitis is a bacterial infection of the postseptal orbital space extending from acute or chronic sinusitis. It can lead to life-threatening complications, such as visual loss, cavernous sinus thrombosis, meningitis, cerebritis, endophthalmitis, and brain abscess. Periorbital cellulitis, on the other hand, involves the preseptal soft tissue of the eyelid and results from trauma or local infection. Both entities feature erythema, induration, tenderness,

and/or warmth, but only orbital cellulitis has proptosis and limited ocular motility. Both commonly affect children; periorbital cellulitis occurs more often in children <5 years of age, and orbital cellulitis occurs more commonly in children >5 years of age.³¹ Evaluation includes blood and skin bacterial cultures that are commonly negative (most likely because of antibiotic administration before admission and laboratory work-up), but if positive grow *Staphylococcus aureus*, *Streptococcus pneumoniae*, or *Staphylococcus epidermiditis*.³¹

Therapy. Children who fail to respond to outpatient systemic antibiotics within 48 to 72 hours are often hospitalized with ophthalmology or ear, nose, and throat specialist consultations for additional work-up and treatment recommendations. First-line therapy is ampicillin/sulbactam followed by clindamycin and cefoxamine.³¹

Mycobacterial

Tuberculosis (*Mycobacterium tuberculosis*)

Key points

- Tuberculosis can spread to the eye hematogenously from the lung or other sites to cause granulomatous disease and inflammation
- All patients with active tuberculosis should be screened by an ophthalmologist

Tuberculosis (TB) affected 9,945 individuals in the United States in 2012, an incidence of 3.2 in 100,000.³² The most common presentation of cutaneous TB, lupus vulgaris, has large red-brown atrophic plaques with telangiectasias on the face, breast, thighs, and eyelids.^{15,33} Pulmonary and extrapulmonary active TB can spread hematogenously to the eye, causing granulomatous intraocular disease and inflammation of the retina or choroid.^{33,34} Patients may report vague symptoms of eye pain and tearing independent of any pulmonary symptoms. The diagnosis of ocular TB is best made by ophthalmology with interferon-gamma release assay and PCR studies of the ocular fluids.³⁵ All patients with active TB should have their eyes screened by an ophthalmologist at the time of their initial diagnosis and with any report of new ocular symptoms.

Therapy. The treatment for TB is systemic multi-drug therapy prescribed by an infectious disease specialist and possible steroids to reduce ocular inflammation prescribed by an ophthalmologist.^{15,33}

Leprosy (*Mycobacterium leprae*)

Key points

- Leprosy causes visual impairment in 5% of affected patients and blindness in 1.3%
- Patients with leprosy and ocular symptoms need ophthalmology referral

Around 2 million people worldwide are affected by leprosy, with 209 new cases reported in the United States in 2009.³⁶ In the skin, tuberculoid leprosy presents with hypopigmented and anesthetic macules or patches, while lepromatous leprosy involves symmetrical papular or nodular lesions, commonly on the nose, ears, hands, and buttocks.¹⁵ The eye can develop low-grade uveitis, dilated pupils, and atrophy of the iris. Later in the disease course (with morphing of the eyelid architecture), patients have keratitis from chronic environmental exposure.³⁴

Ocular involvement is more common in lepromatous than tuberculoid leprosy.³⁷ A study conducted on 311 leprosy patients in Northern Nigeria revealed bilateral visual impairment in 5.1% and total blindness in 1.3% of patients.³⁸ Cited causes for blindness included exposure keratitis (21.3%), corneal opacities (13.5%), and chronic uveitis (10.1%). Eye symptoms should be carefully sought out in leprosy patients and, if present, should prompt referral to an ophthalmologist to prevent permanent blindness.³⁸

Therapy. Leprosy, once confirmed by skin biopsy or PCR studies, requires systemic multidrug treatment that is usually prescribed in consultation with an infectious disease specialist.³⁷ The use of topical steroid eye drops and phenylephrine helps keep pupils mobile, preventing scarring and blindness.¹⁵

Parasitic

Onchocerciasis (*Onchocerca volvulus*)

Key point

- Onchocerciasis causes “river blindness,” a major cause of blindness in equatorial Africa and parts of Central/South America where its vector, the Simulium fly, is found

Onchocerciasis is a parasite-mediated disease endemic in regions with the Simulium fly, including equatorial Africa and Yemen and certain areas of Central and South America.¹⁵ It causes “river blindness,” a major cause of blindness worldwide. The initial presentation involves intense pruritus and intraepithelial abscesses containing microfilariae.^{15,39} The skin subsequently becomes dry and atrophic with nontender subcutaneous nodules containing adult worms.⁴⁰ The microfilariae evoke an inflammatory response, with edema and injection of the eyes leading to cicatricial keratitis with resultant loss of vision.^{15,40} Patients may also complain of floating black spots, eye pain, photophobia, or excessive tearing, suggestive of anterior uveitis or chorioretinitis, which are both commonly seen in patients with onchocerciasis.

If infection is suspected without evidence of skin parasites, an ophthalmologic examination may help confirm the diagnosis.¹⁵ *O. volvulus* microfilariae can be seen in the inferior angle of the anterior chamber of the eye with gonioscopy (ie, the use of a prism or lens to view the angle of the anterior chamber) or slit lamp examination.¹⁵

Therapy. One dose of oral ivermectin (150 µg/kg) decreases microfilariae in the anterior chamber and cornea for up to 1 year, with ongoing improvement of ocular damage documented up to 24 months after treatment.⁴¹ As with most destructive infectious processes, earlier treatment increases a patient’s chance for full visual recovery. The World Health Organization recommends an annual single dose of oral ivermectin in endemic countries to reduce the prevalence.^{15,42}

Schistosomiasis (*Schistosoma mansoni*, *Schistosoma haematobium*, and *Schistosoma japonicum*)

Key points

- The eggs of schistosomiasis can cause an inflammatory granulomatous reaction in all organ systems, including the skin and eye
- Physicians must consider this parasitic infection in any traveler returning from an endemic area given the widespread sequelae

Schistosomiasis is a flatworm parasite endemic in parts of Asia, sub-Saharan Africa, and Japan. Humans are exposed by swimming in freshwater lakes or rivers in endemic regions. The parasite penetrates the human skin and resides in large veins, where it lays eggs.⁴³ These eggs may travel throughout the body hematogenously and can trigger a granulomatous inflammatory response in any organ. In the skin, there may be early mild pruritus (swimmer’s itch), later perineal or genital granulomas with fistulas, or chronic skin-colored papules and nodules on the trunk.⁴³ If deposited in the eye, uveitis and subretinal granulomas develop.⁴⁴ Schistosomiasis is diagnosed by identification of the causative eggs in the feces, urine, or eye and by skin biopsy specimens of appropriate lesions.

Therapy. Schistosomiasis is treated with a single course of oral praziquantel (20 mg/kg TID for 1 day).^{43,44}

INFLAMMATORY DISEASE

A summary of eye findings in inflammatory oculocutaneous diseases and recommendations on when to refer the patient to an ophthalmologist if they have signs/symptoms of ocular disease can be seen in Table III.

Table III. Summary of eye findings in inflammatory oculocutaneous diseases and recommendations on when to refer to an ophthalmologist if a patient has signs/symptoms of ocular disease

Inflammatory disease	Ocular manifestations	Referral time*
Common		
Rosacea	Dry eye, blepharitis, and hordeola/chalazia	Nonurgent
Atopic dermatitis	Keratoconjunctivitis (pruritic eyes)	Nonurgent
Contact dermatitis	Eyelid erythema, pruritus, and scale	Nonurgent
Psoriasis	Dry eye, blepharitis, and chronic conjunctivitis	Nonurgent
Bullous		
Mucous membrane pemphigoid	Conjunctivitis and ulceration	Urgent
Pemphigus vulgaris	Scarring conjunctivitis and vasculitis	Nonurgent
Linear immunoglobulin A disease	Dry eye, burning, and foreign body sensation	Urgent
Epidermolysis bullosa acquisita	Syblepharon	Nonurgent
Paraneoplastic pemphigus	Conjunctivitis, corneal melting, and perforation	Urgent
Behcet disease	Uveitis (unilateral early on)	Urgent
Connective tissue disease		
Systemic lupus erythematosus	Dry eye	Nonurgent
Systemic sclerosis	Keratoconjunctivitis sicca, itching, and dry eye	Nonurgent
Sjögren syndrome	Keratoconjunctivitis sicca and dry eye	Urgent or Nonurgent
Miscellaneous		
Sarcoidosis	Uveitis	Nonurgent
Amyloidosis	Waxy hemorrhagic papules on eyelid and ptosis	Nonurgent
Graft versus host disease (acute)	Corneal sloughing, dry eye, pseudomembranous conjunctivitis, and serosanguineous discharge	Urgent
Graft versus host disease (chronic)	Cicatricial ectropion, conjunctivitis, dry eye, lid scarring, and syblepharon	Urgent

*Immediate: same day as presentation; urgent: same week as presentation; nonurgent: when available.

Common conditions

Rosacea

Key points

- Patients with ocular symptoms and rosacea may benefit from systemic antibiotic treatment, artificial tears, and warm compresses
- Hordeola and chalazia are associated with rosacea, but may occur independent of rosacea and are best treated with warm compresses

Rosacea is a common skin disorder affecting up to 10% of adults. More than half of these cases have ocular involvement independent of skin severity.^{45,46} Facial skin has inflammatory papules and pustules, facial redness, erythema, and occasionally phymatous changes. Similar redness and telangiectasia can be seen on the eyelid with blepharitis, hordeola, and chalazia along the eyelid margin. Dry eye, corneal erosions, and bacterial colonization can occur within the eye.^{45,46} Patients may complain of ocular pain, burning, foreign body sensation, and dryness.^{45,47} The diagnosis of cutaneous rosacea and ocular rosacea can be made clinically, but any symptomatic eye involvement should prompt an ophthalmology referral and appropriate treatment should be decided jointly between the departments of dermatology and ophthalmology.

Therapy. Ocular rosacea requires systemic treatment with oral antibiotics, such as doxycycline (100 mg twice daily for 6–8 weeks then daily for 3 months). Topical antibiotic ointments, such as erythromycin or bacitracin 1 to 2 times daily, will help reduce bacterial colonization.⁴⁵ Warm compresses are useful in unplugging the clogged meibomian glands involved in hordeola and chalazia. Gentle washing with baby shampoo or a gentle nonsoap facial cleanser can also remove oil and debris from the eyelid margins. Scrubbing, picking, and rubbing must be avoided, and in severe cases incision and drainage may be required.⁴⁷ Preservative-free artificial tears up to 4 times daily are recommended for dry eyes.⁴⁵ If oculocutaneous symptoms persist, low-dose isotretinoin can be beneficial.⁴⁸ Cyclosporin eye drops (Restasis; Allergan, Irvine, CA) used twice daily or reversible silicone punctal plugs are also very helpful with dry eyes. All patients with keratitis, iritis, or scleritis benefit from referral to the ophthalmology department for evaluation and possible use of ophthalmic medications.⁴⁸

Atopic dermatitis

Key points

- Atopic dermatitis involves the eye in 25% to 40% of patients
- Ophthalmologists treat keratoconjunctivitis (allergic conjunctivitis) with corticosteroid

ophthalmic drops, intraocular antihistamine drops, and intraocular mast cell stabilizers—agents that are not commonly prescribed by dermatologists

Ocular involvement of atopic dermatitis (AD) occurs in 25% to 40% of cases. AD patients frequently have eyelid dermatitis as part of their skin disease, but also suffer from intraocular complications, such as atopic keratoconjunctivitis (also referred to as allergic conjunctivitis) and cataracts. Atopic keratoconjunctivitis is the most common and potentially most severe complication of AD. It presents with bilateral eye itching, eye fatigue, irritation, and a foreign body sensation.⁴⁹ It may progress to ulceration and corneal perforation. Less commonly, anterior subcapsular cataracts can occur as part of AD, while posterior subcapsular cataracts can form after treatment with systemic steroids. In addition, AD patients are at risk of keratoconus (protrusion of central part of cornea) and corneal thinning from constant rubbing of their eyes. Ophthalmologic referral is appropriate for AD patients with ocular or periocular symptoms.

Therapy. Dermatologists can manage eyelid AD with gentle cleansers, wet compresses, antihistamines, emollients, and low-potency topical steroids. Tacrolimus 0.03% ointment is a nonsteroidal immunomodulating agent used twice daily and is considered safe for use on the eyelid in AD.^{50,51} Ophthalmologists typically manage atopic keratoconjunctivitis with intraocular corticosteroid ophthalmic drops and ointment, intraocular antihistamine drops, and intraocular mast cell stabilizers (eg, olopatadine or ketotifen).⁴⁵

Allergic contact dermatitis

Key points

- The thin skin of the eyelid predisposes it to multiple allergens, making identification of the specific inciting agent difficult
- Traditional patch testing helps identify a causative allergen in approximately 50% of cases

The thin skin of the eyelids makes them particularly susceptible to allergic contact dermatitis (ACD).⁵² Eyelid ACD presents with pruritic, erythematous, and scaly plaques with or without secondary lichenification (Fig 5). Allergen exposures range broadly and include metals, nail polish, airborne pollens, over the counter products, prescription eye drops, etc.⁵² Standard patch testing will identify the inciting allergen in approximately 50% of cases. This increases when the patient is patch tested to samples of his/her own products.⁵³



Fig 5. Contact dermatitis. A young patient with allergic contact dermatitis caused by swimming goggles. (Photograph courtesy of Fred Ghali, MD.)

Therapy. Treatment includes low-potency topical steroids or topical calcineurin inhibitors (eg, tacrolimus and pimecrolimus) for 2 to 3 weeks and removal of the allergen (if identified).⁵² Cold compresses, preservative-free lubricating tears, and topical preservative-free steroid ointment, such as ioteprednol (Lotemax; Bausch and Lomb, Berlin, Germany), bring relief to the patient.

Psoriasis

Key points

- Intraocular psoriasis is frequently asymptomatic
- Dry eye is reported in approximately 1 of 5 psoriasis patients
- Intraocular corticosteroid and lubricating eye drops are indicated for intraocular psoriasis, while low-potency steroids or calcineurin inhibitors are appropriate for eyelid plaques

The prevalence of ocular psoriasis has not been well studied, but expert opinion reports an incidence of 10% for all psoriasis patients and >30% in patients with psoriatic arthritis.^{54,55} Well demarcated erythematous scaly plaques frequently form on the eyelid (especially close to the medial canthus) with secondary swelling, crusting, flaking, and scales adherent to the lashes. Dry eyes are reported in up to 18% of psoriasis patients compared to 6.7% to 14.6% reported in the general population.⁵⁶ Patients frequently complain of burning and itching, suggestive of an underlying blepharitis caused by meibomian gland occlusion by psoriatic scale. This may cause visual impairment if left untreated. Independent of the eyelid psoriasis, chronic conjunctivitis can occur and is characterized by a thick yellow discharge, tearing, and redness.⁵⁷ This chronic conjunctivitis can lead to more painful corneal keratitis and scarring.⁵⁷ Uveitis is another

serious complication that is reported in 7% to 20% of psoriasis patients, with a far higher prevalence (32%) among patients with psoriatic arthritis or other spondyloarthropathies (eg, reactive arthritis, ankylosing spondylitis, and arthritis associated with inflammatory bowel disease).^{54,55}

The diagnosis of intraocular psoriasis requires an ophthalmologic examination. Therefore, dermatologists should conduct an ocular review of systems with all new psoriasis patients and those with a recent flare. Questions should include inquiries regarding eye discomfort, dryness, crusting or flaking of the eyelashes, swollen or painful eyelids, red eyes, lid plaques, and changes in vision. Some experts do suggest routine eye screening for patients with severe psoriasis.⁵⁴

Therapy. Cutaneous ocular psoriasis is treated topically with low-potency topical steroids and/or topical calcineurin inhibitors. The majority of intraocular psoriatic conditions are treated with ophthalmic topical steroids and lubricating eye drops.⁵⁷

Bullous diseases

Mucous membrane pemphigoid

Key points

- Eighty percent of ocular mucous membrane pemphigoid cases are caused by autoantibodies against $\alpha 6\beta 4$ integrin ($\beta 4$ more than $\alpha 6$)
- Ocular mucous membrane pemphigoid is divided into 4 progressive clinical stages
- It is most often diagnosed in stage III and requires urgent immunosuppressive therapy to prevent scarring conjunctivitis and blindness

Mucous membrane pemphigoid (MMP) is the most common cutaneous blistering disorder affecting the eye. Up to 80% of MMP patients have ocular involvement caused by antibodies directed at the $\alpha 6\beta 4$ integrin, with the $\beta 4$ subunit being the most common antigen.⁵⁸ The resulting blister is located at the level of the lamina lucida at the dermoepidermal junction as seen by fine linear immune globulin (IgG) and complement (C3) deposition at the basement membrane on direct immunofluorescence.^{59,60}

Ocular MMP causes progressive cicatrizing conjunctivitis, resulting in corneal ulceration, scarring, and even blindness (Fig 6). Patients complain of itching, burning, or a foreign body sensation in their eyes. The clinical course of MMP is divided into 4 stages (Table IV).^{58,59,61} Ideally, the diagnosis should be made in stages I and II. However, most MMP patients are diagnosed in stage



Fig 6. Resultant scarring from progressive cicatrizing conjunctivitis seen in ocular mucous membrane pemphigoid.

III and should therefore be treated immediately with aggressive immunosuppressive therapy.⁵⁸

Therapy. All MMP patients should be screened immediately for eye symptoms, including itching, burning, eyelash abnormalities, and a foreign body sensation in their eyes, and prompt referral should be made to the ophthalmology department if any ocular symptoms are reported. The first-line treatment of isolated ocular MMP is oral dapsone, but oral corticosteroids are indicated if blisters involve other regions of the body.⁶² Alternative steroid-sparing treatments for MMP include mycophenolate mofetil, sulfasalazine, methotrexate, and azathioprine.^{59,61}

Pemphigus vulgaris

Key point

- Pemphigus vulgaris typically involves both the skin and the oral mucosa

Thirty cases of ocular pemphigus vulgaris have been reported in the literature involving non-scarring conjunctivitis without long-term visual sequelae.^{61,63} It is recommended that consideration be given for referral to ophthalmology in patients with ocular symptoms and pemphigus vulgaris.⁶³

Therapy. Systemic treatment of pemphigus vulgaris has historically involved oral steroids in conjunction with steroid-sparing agents, such as cyclophosphamide or azathioprine, with rituximab showing significant benefit in recent studies.^{64,65}

Linear immunoglobulin A disease

Key point

- Half of linear immunoglobulin A disease patients have eye symptoms and require slit lamp examination by an ophthalmologist to screen for conjunctival and corneal changes

Linear immunoglobulin A disease (LAD) is caused by an antibody directed at the 97-kD ectodomain of bullous pemphigoid antigen 2. Dermatologic signs of LAD classically include tense annular bullae

Table IV. Ocular findings in each stage of mucous membrane pemphigoid

Stage	Ocular findings
I	Subepithelial fibrosis and inflammation
II	Shrinking of the conjunctiva causes shortening of the fornices and loss of goblet cells
III	Symblepharon, with adhesion of the palpebral conjunctiva reflected onto the eyelid to the bulbar conjunctiva, and covering the globe
IV (end stage)	Ankyloblepharon (eyelid adhesions), entropion (eyelid inversion), severe dry eye from scarred lacrimal glands, cornification of the ocular surface, and scarring. Trichiasis (inward growth of the eyelashes) follows and can lead to further corneal abrasion, ulceration and blindness

resembling a “string of pearls” on a patch of erythematous skin with or without mucous membrane involvement. Approximately half of LAD patients have eye symptoms such as dry eyes, foreign body sensation, burning, and/or discharge.⁶¹ Slit lamp examination by an ophthalmologist reveals conjunctival scarring and subconjunctival fibrosis with some secondary corneal clouding that can cause a long-term decline of vision.⁶¹

Direct immunofluorescence studies reveal a linear deposition of immunoglobulin A at the dermoepidermal junction.

Therapy. Treatment of both cutaneous and ocular LAD involves discontinuation of any inciting drugs (eg, vancomycin), several weeks of dapsone or sulfapyridine, and treatment of superinfection with topical antibiotics.⁶¹

Epidermolysis bullosa acquisita

Key point

- **Epidermolysis bullosa acquisita can cause symblepharon and blindness**

Epidermolysis bullosa acquisita (EBA) is caused by acquired immunity to the NC-1 domain of collagen VII, resulting in a subepidermal cutaneous split. Direct immunofluorescence studies reveal linear IgG and C3 in a U-shaped serrated pattern at the dermoepidermal junction with the fluorescence on the floor in salt-split skin. The most common oculocutaneous finding of EBA is symblepharon, with severe cases causing blindness.^{61,66} Case reports have suggested that the IgA subtype of EBA is more likely to produce severe eye involvement and potentially be refractory to treatment, resulting in permanent visual compromise.⁶⁷ Therefore, all patients

with EBA should be evaluated by an ophthalmologist for these complications.

Therapy. Colchicine may be used as adjunctive therapy for ocular involvement in addition to immunomodulating treatments, including dapsone, prednisone, azathioprine, cyclophosphamide, methotrexate, and cyclosporine.^{61,67}

Paraneoplastic pemphigus

Key points

- **Paraneoplastic pemphigus is most commonly associated with hematologic malignancies with resultant autoantibodies against a variety of desmosomal proteins**
- **Paraneoplastic pemphigus causes scarring corneal changes, so prompt referral is indicated upon diagnosis**

Paraneoplastic pemphigus (PNP) is a severe autoimmune disorder associated with an array of underlying malignancies, the most common being non-Hodgkin’s lymphoma. Patients with PNP typically present with polymorphic cutaneous bullous lesions and severe mucous membrane disease, most commonly desquamative gingivitis extending onto the vermillion border. PNP is caused by autoantibodies targeting envoplakin, periplakin, desmoplakin, bullous pemphigoid antigen 1, plectin, or plakoglobin. Ocular involvement is found in 66% to 72% of patients with PNP. The typical presentation includes conjunctivitis that can progress to cicatrizing disease.⁶⁸ In addition, corneal thinning and perforation have also been observed.⁶⁹ Once the patient has progressed to end-stage scarring of the cornea, response to therapy is extremely poor. Therefore, early referral of patients with PNP to an ophthalmologist is essential once the diagnosis is confirmed.⁷⁰

Diagnosis is confirmed with a biopsy specimen that reveals suprabasal acantholysis with dyskeratosis, direct immunofluorescence studies with IgG and C3 deposited intercellularly and at the dermoepidermal junction, and indirect immunofluorescence with intercellular IgG on rat bladder transitional epithelium.⁷⁰

Therapy. Cyclosporine, corticosteroids, and azathioprine have shown minimal success in PNP compared to treatment for pemphigus vulgaris.⁷⁰ Progression of PNP is largely dependent on the nature of the underlying neoplasm; therefore, diagnosis and treatment of the underlying neoplasm is of the utmost importance.⁷⁰

Behçet disease

Key points

- **Uveitis is a minor diagnostic criterion of Behçet disease and is seen in 70% to 85% of cases**

- Visual loss is seen after 3 years, and 25% of patients with ocular Behçet disease develop blindness within 5 years if untreated

Behçet disease is a multisystem vasculitis that presents with recurrent oral ulcers, genital ulcers, skin changes, and uveitis.^{71,72} Cutaneous involvement is variable and can include erythema nodosum or pyoderma gangrenosum-like lesions. Ocular manifestations occur in 70% to 85% of cases, with resulting visual loss after approximately 3 years.⁷³ While oral aphthae-like ulcers are usually the first finding of Behçet disease, unilateral uveitis may precede the mucosal ulcers.⁷² Early eye involvement is unilateral, with two-thirds of patients progressing to bilateral eye disease.⁷¹ Up to 25% of patients with affected eyes develop blindness caused by occlusive vasculitis and an inflammatory glaucoma that results in necrotizing retinal disease and optic nerve atrophy, respectively (Fig 7).^{72,73} These chronic sequelae and complications may be so severe that enucleation may be necessary. It takes <5 years to progress from the onset of ocular symptoms to blindness.^{72,73} Therefore, prompt evaluation by an ophthalmologist is essential for all patients with Behçet disease.

The major criterion for diagnosis of Behçet disease is >3 episodes of oral ulceration within 12 months with at least 2 minor criteria: genital ulceration, cutaneous lesions, and pathergy.⁷⁴

Therapy. Treatment of Behçet disease ranges from topical corticosteroids to more aggressive immunosuppressive agents. Azathioprine has been shown to prevent the development of ocular disease when compared to placebo.⁷² Systemic cyclosporine is used to treat uveitis and improves visual acuity. It is superior to systemic colchicine for decreasing frequency and severity of eye attacks.⁷² Interferon-alfa causes complete remission of ocular vasculitis in the majority of patients. Tumor necrosis factor-alfa inhibitors did not show significant ocular improvement.⁷² Selection of appropriate therapy should take into consideration all aspects of the disease, costs, and associated risks to the patient.

Connective tissue diseases

Systemic lupus erythematosus

Key points

- The eyes are affected in 30% to 50% of patients with systemic lupus erythematosus
- Dry eye is the most common finding, followed by retinopathy and drug-induced complications

Systemic lupus erythematosus (SLE) is an autoimmune disorder that can affect any organ system.

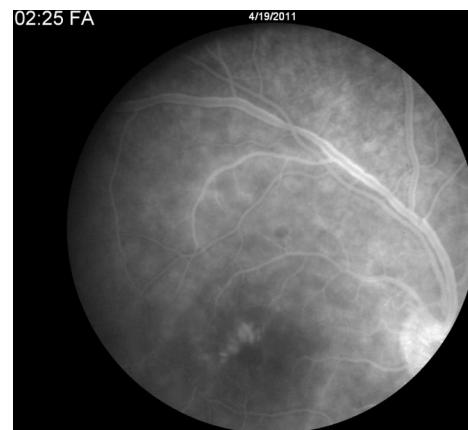


Fig 7. Fluorescein angiogram of a patient with Behçet disease at 2:25 minutes showing mild cystoid macular edema with retinal vasculitis. (Photograph courtesy of Robert Wang, MD.)

The reported prevalence of eye disease in SLE is 34% to 47%.^{75,76} An SLE study from a tertiary eye care center in Nepal reported that the most common presentations of ocular SLE include dry eye (39.5%), lupus retinopathy (21%), and drug-induced ocular complications (21%).⁷⁵ Patients with lupus retinopathy may complain of blurred vision, floaters, or blind spots. In addition, lupus vasculitis can affect the retinal vessels, and patients with antiphospholipid antibodies are at an increased risk for developing retinal vaso-occlusive disease (Fig 8). It is recommended that all patients with antiphospholipid antibodies have an ophthalmologic referral, along with SLE patients who develop eye pain or acute visual changes.

Therapy. Patients with lupus are frequently treated with hydroxychloroquine, which can also cause retinal problems (see Part II), necessitating routine screening at baseline and annually.⁷⁷

Systemic sclerosis

Key point

- The majority of patients with systemic sclerosis have eye involvement, including dry eye, eyelid skin changes, retinal microvascular occlusions, cataracts, and glaucoma

Systemic sclerosis is an idiopathic autoimmune connective tissue disease that is characterized by sclerotic tightening of the skin. However, the connective tissue of any organ can be affected. Skin changes often begin with Raynaud phenomenon, telangiectasias, symmetrical distal tightening of the skin, and progress to painful ulceration and joint contractures.⁷⁴ A study of 45 systemic sclerosis patients reported 51.1% of patients with eyelid skin changes, 48.9% with keratoconjunctivitis sicca,

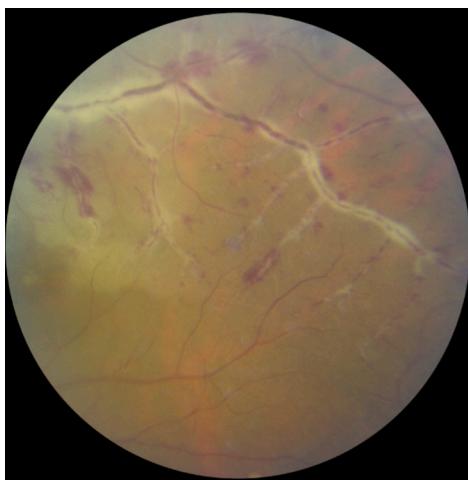


Fig 8. Systemic lupus erythematosus. Severe lupus vasculitis.

42.2% with cataracts, 28.9% with retinal microvascular abnormalities, and 13.3% with glaucoma.⁷⁸ While the cataracts and microvascular changes may be confounded by age, the other findings were thought to be directly related to systemic sclerosis. Patients commonly complain of dry eyes, itching, burning, foreign body sensation, and redness.⁷⁸ Tightening of the skin around the eye can predispose patients to corneal abrasions and infections.⁷⁸

With frequent renal, pulmonary, and cardiac involvement, other subspecialty referrals are also appropriate for complete evaluation and work-up of a patient diagnosed with systemic sclerosis.⁷⁴

Therapy. Systemic sclerosis is often treated with immunomodulating agents, but importantly is individualized based on the extent and location of other involved organ systems.⁷⁴ Preservative-free artificial tears help alleviate dryness; however, if symptoms persist or are severe, patients require an ophthalmologic referral.⁷⁹

Sjögren syndrome

Key point

- **Keratoconjunctivitis sicca is severe dry eye and a major criterion for diagnosis of Sjögren syndrome**

Sjögren syndrome is characterized by dry eyes (keratoconjunctivitis sicca) and dry mouth (xerostomia). More than 3 months of dry eyes and decreased tear production are part of the diagnostic criteria. Patients frequently describe a sandpaper-like feeling in their eyes without cutaneous periocular changes.⁸⁰ Other common complaints are tearing, redness, tiredness or strain, blurred vision, or fluctuating vision along with intolerance to contact lenses.

Therapy. Treatment recommendations include pilocarpine and cevimeline for milder sicca symptoms

and topical cyclosporine for severe keratoconjunctivitis sicca.⁸⁰ Ophthalmologists have had success with 2 additional modalities: (1) reversible silicone punctal plugs that are placed in the inferior and/or superior puncta of the eyelids and (2) autologous serum eye drops derived from the patient's own blood. Rituximab has been suggested as a treatment; however, larger, controlled trials are still necessary to establish its efficacy.⁸⁰

Miscellaneous

Sarcoidosis

Key points

- **Sarcoidosis is associated with a wide variety of ocular presentations with the potential for rapid and devastating visual loss**
- **Twelve percent of sarcoidosis patients have ocular involvement, stressing the importance of an ophthalmologic consultation**

Sarcoidosis is a noncaseating granulomatous disease that is thought to be triggered by an immunologic response to an unknown environmental trigger.⁸¹ There is high variability in the presentation of sarcoid, ranging from isolated cutaneous lesions to systemic multiorgan involvement and even death. More than 90% of patients have a nonproductive cough or wheeze, 24% will have skin findings, and 12% ocular involvement.⁸² Erythema nodosum, dyspigmentation, and lupus pernio (violaceous nodules of chronic sarcoid) are seen on the skin, while the eye most commonly develops an anterior, intermediate, or posterior uveitis (Fig 9).^{81,83} Visual loss from sarcoidosis can occur with or without ocular symptoms; dermatologists should therefore refer all sarcoid patients to the ophthalmology department upon the initial diagnosis and inquire about new ocular symptoms at each follow-up.⁸⁴

Therapy. Acute multiorgan sarcoidosis is treated initially with systemic corticosteroids. Once chronic treatment is indicated (with or without ocular involvement), methotrexate, azathioprine, and mycophenolate mofetil are recommended, with new data emerging supporting an important role for tumor necrosis factor-alfa inhibitors.^{84,85} Treatment of ocular sarcoidosis alone varies from topical corticosteroids for mild uveitis, periocular corticosteroid injections for persistent ocular disease, and steroid-sparing immunosuppressive agents for patients requiring >4 periocular injections a year given the high risk of glaucoma associated with steroids (see Part II).⁸¹

Amyloidosis

Key points

- **Amyloid can deposit in and/or around the eye, causing a variety of sequelae**



Fig 9. Sarcoidosis. Cutaneous sarcoid with characteristic red-brown granulomatous papules along the eyelid and nose.

- **Ophthalmology surgery may be indicated for some forms of ocular amyloid**

Amyloidosis is the term for a group of protein deposition disorders that can be primary, secondary, or hereditary and can affect any organ system. Although the early findings in primary systemic amyloidosis are nonspecific—such as weight loss or fatigue—dermatologists should consider amyloidosis when a patient has petechiae/ecchymoses, waxy dermal papules, tongue thickening with carpal tunnel, and/or patchy hair loss.⁷⁴ Amyloid can affect any part of the eye and periocular tissue. Periocular involvement is commonly a palpable mass or infiltration with associated ptosis.⁸⁶ When the eyelids are affected, they have waxy hemorrhagic deposits, often reflecting underlying systemic involvement and warranting additional work-up. Intraocular involvement can be variable according to the classification of underlying amyloid disease, and includes conjunctival deposits, glaucoma, scalloped border pupils, nerve compression, and retinal hemorrhage.⁸⁶

Therapy. A patient with any ocular signs or symptoms associated with known amyloidosis should be referred to the ophthalmology department for evaluation and possible surgical intervention.⁸⁶

Graft versus host disease

Key points

- **Graft versus host disease is a common complication of allogenic hematologic stem cell transplantation**
- **In acute graft versus host disease, 40% to 60% of patients develop ocular involvement. This increases to up to 70% in chronic graft versus host disease**

Hematologic stem cell transplantation (HSCT) is a widely used therapy for the treatment of a variety of hematologic disorders. Graft versus host disease

(GVHD) is a common and significant side effect.⁸⁷ The risk of GVHD is lowest among identical twins, increases to 30% to 40% if the donor is a relative, and ranges from 60% to 80% if there is no relation between donor and recipient.⁸⁸

GVHD is divided into 2 categories: acute and chronic, both of which can involve the eye and/or skin. Acute GVHD typically occurs within the first 100 days posttransplant with associated erythematous or bullous cutaneous eruption.⁸⁷ Chronic GVHD is associated with the loss of normal immune regulation mechanisms, resulting in cutaneous lichenoid and/or sclerodermatosus changes.^{87,89} Ocular manifestations are found in 40% to 60% of patients with acute GVHD and up to 69% to 77% of patients with chronic GVHD (Table V).⁸⁷

It is essential for dermatologists to ask post-HSCT patients about eye irritation and visual changes in addition to completing a thorough skin examination. The severity of both cutaneous and ocular GVHD mirrors the extent of systemic GVHD.^{87,89} If GVHD is suspected, it is imperative that the patient be referred to his or her ophthalmologist and oncologist as soon as possible.

Therapy. The treatment of ocular GVHD focuses on lubrication, reduction of inflammation, and epithelial support. Artificial tears, cyclosporine eye drops, steroids, tacrolimus, oral tetracyclines, tarsorrhaphy, and erythromycin ointment are among the many medications used for the treatment of ocular GVHD. Prevention and prophylaxis, however, remain the mainstay therapy for GVHD. This involves optimal human leukocyte antigen matching and appropriate immune suppression with drugs such as tacrolimus, methotrexate, and corticosteroids.⁸⁷

GENODERMATOSES

A summary of eye findings in oculocutaneous genodermatoses and recommendations as to when to refer to an ophthalmologist if a patient has signs/symptoms of ocular disease is shown in Table VI.

Associated with pigment abnormalities

Incontinentia pigmenti

Key point

- **Patients with incontinentia pigmenti have dental (80%), neurologic (30%), and ocular (25-70%) involvement in addition to their skin changes necessitating coordination of care among specialists**

Incontinentia pigmenti (IP), also known as Bloch–Sulzberger syndrome, is a rare X-linked dominant disorder caused by the mutation of the

Table V. Ocular manifestations of graft versus host disease

Type of GVHD	Ocular manifestations
Acute	Most common: Keratoconjunctivitis sicca caused by the accumulation of a PAS-positive material causing stasis in the lacrimal gland Also: Hyperemic conjunctiva, serosanguineous discharge, pseudomembranous conjunctivitis, and corneal epithelial sloughing
Chronic	Most common: Dry-eye secondary to fibrotic destruction of the tubuloalveolar glands leading to pruritus, burning, foreign body sensation, and blurred vision Also: Conjunctivitis, palpebral conjunctival fibrovascular changes with or without epithelial sloughing, lid scarring, cicatricial entropion, and symblepharon

GVHD, Graft versus host disease; PAS, periodic acid-Schiff.

nuclear factor- κ light chain-enhancer of activated B cells essential modulator gene (NEMO) located on the X chromosome.^{90,91} Skin changes in IP progress through 4 sequential stages, from (1) erythematous vesicular lesions along the lines of Blaschko 2 to 8 weeks after birth, to (2) verrucous lesions on the distal limbs, then (3) whorled slate grey-brown hyperpigmentation by childhood, and ultimately regress to (4) wavy, hypopigmented, occasionally anhidrotic hairless macules.^{91,92} About 80% of IP patients have dental abnormalities (pegged teeth), with neurologic impairment in 30% of patients (ie, seizures or severe global mental retardation).⁹³ Ocular abnormalities are seen in 25% to 70% of IP patients and include strabismus, congenital cataracts, and retinal vascular abnormalities resembling retinopathy of prematurity.

Therapy. Ophthalmology referral on initial presentation is imperative to prevent ocular nerve atrophy with interventions such as corrective lenses and cataract surgery.^{91,94} Coordination of care is integral for IP patients and should involve a dermatologist, ophthalmologist, pediatrician, neurologist, geneticist, and dentist.⁹²

Oculocutaneous albinism

Key point

- Patients born with oculocutaneous albinism develop nystagmus, strabismus, photophobia, and foveal hypoplasia in early infancy and childhood requiring early evaluation and treatment by an ophthalmologist

Oculocutaneous albinism (OCA) is a group of autosomal recessive disorders with mutations in the

melanin synthesis pathway resulting in altered ocular, cutaneous, and pilar pigmentation (Table VII).^{95,96} OCA type 1 is more severe and has a complete lack of melanin pigment in the skin, hair, and eyes, but type 2 OCA patients develop pigmentation with age.⁹⁵ The eyes of OCA patients typically lack pigment and are blue-grey at birth.⁷⁴ While cutaneous neoplasms are often the major concern in OCA, ocular complications to consider in the first year of life include nystagmus, strabismus, photophobia, and foveal hypoplasia with concomitant poor vision.⁹⁶ Underdeveloped optic tracts lead to learning difficulties and persistent neurologic visual processing abnormalities in affected children. Ophthalmologic referral is necessary for all patients.

Therapy. The management of OCA focuses on glasses (to improve vision), photoprotection to minimize cancer risk, and the appropriate early treatment of skin cancers.⁹⁵

Hermansky-Pudlak syndrome

Key points

- **Hermansky-Pudlak syndrome affects organelle function, resulting in impaired trafficking of melanosomes and impaired platelet function**
- **Ocular findings of Hermansky-Pudlak syndrome are similar to those of oculocutaneous albinism**

Hermansky-Pudlak syndrome (HPS) is an autosomal recessive disorder with 8 identified gene mutations affecting membrane trafficking proteins and resulting in altered intracellular secretary organelle function.⁹⁷ Most commonly, it is caused by mutations in HPS1 and HPS3 genes.⁹⁸ HPS is extremely rare among the general population except for Puerto Ricans, who have a prevalence of 1 in 1800.^{97,99} Patients are often neutropenic and suffer from pulmonary fibrosis, colitis, and bleeding disorders (platelet dysfunction caused by a lack of dense granules).^{97,99} Skin and eye findings are similar to OCA with hypopigmentation of the skin, hair, and eyes, along with nystagmus and decreased visual acuity (Table VII).⁹⁹

Therapy. While there are no specific treatments for HPS, patients should receive preprocedural platelets and regular ophthalmologic care.¹⁰⁰

Chediak-Higashi syndrome

Key point

- Melanosomes accumulate within melanocytes, causing hypopigmentation and similar ocular findings as those seen with oculocutaneous albinism

Chediak-Higashi syndrome (CHS) is a rare autosomal recessive disorder caused by a mutation

Table VI. Summary of eye findings in oculocutaneous genodermatoses and recommendations on when to refer to an ophthalmologist if a patient has signs/symptoms of ocular disease

Genodermatoses	Ocular manifestations	Referral time*
Pigment abnormalities		
Incontinentia pigmenti	Strabismus, congenital cataracts, and retinal vascular abnormalities	Urgent
OCA	Blue-grey irides, photosensitivity, strabismus, and poor foveal and macular development	Nonurgent
Hermansky-Pudlak	Similar to OCA, also with decreased visual acuity and nystagmas	Nonurgent
Chediak-Higashi	Nystagmus, photophobia, and decreased visual acuity	Nonurgent
Waardenburg	Heterochromic iris and dystopia canthorum	Nonurgent
Disorders of keratinization		
Ichthyosis	Ectropion, madarosis, and conjunctivitis	Nonurgent
X-linked ichthyosis	White, comma-shaped opacities in the Descemet membrane	Nonurgent
KID syndrome	Photophobia, dry eye, and neovascularization of cornea	Nonurgent
IFAP syndrome	Photophobia and corneal ulceration	Nonurgent
Refrsum	Retinitis pigmentosa	Nonurgent
Richner-Hanhart	Severe keratitis, corneal ulceration, and neovascularization of cornea	Urgent
Associated with neoplasms		
Basal cell nevus syndrome	Cataracts, hamartoma of the retina, and nystagmus	Urgent
Xeroderma pigmentosum	Eyelid tumors, corneal opacification, exposure keratitis, pterygium, photophobia, and chronic conjunctival injection	Urgent
Miscellaneous		
Pseudoxanthoma elasticum	Angoid streaks	Nonurgent
Fabry disease	Whorled corneal opacity	Nonurgent

IFAP, Ichthyosis follicularis alopecia and photophobia; KID, keratitis-ichthyosis-deafness; OCA, oculocutaneous albinism.

*Immediate: same day as presentation; urgent: same week as presentation; nonurgent: when available.

in the LYST gene leading to accumulation of lysosomal granular inclusions in a variety of cell types including melanocytes, platelets, neutrophils, and nerves (Table VII).¹⁰¹ In addition to severe bacterial infections, a tendency to bruise, and peripheral neuropathy, patients with CHS have decreased pigment in their skin, hair, and eyes, similar to OCA.⁹⁹ Cutaneous manifestations include white to grey skin with discrete nevi and lentigines on sun-exposed areas. The hair is classically metallic silver.¹⁰¹ Eyes are grey-blue or brown, and patients have nystagmus, photophobia, and decreased visual acuity. CHS is diagnosed microscopically by the presence of giant peroxidase-positive granules in leukocytes, megakaryocytes, neurons, conjunctival fibroblasts, and cultured lymphoblasts.¹⁰¹

Therapy. Bone marrow transplant is the only reported curative treatment for CHS.¹⁰¹ Children should receive a full vaccination schedule, take antibiotics for the recurrent infections, and avoid aspirin. Immunomodulating agents, such as corticosteroids, intravenous immunoglobulin, and splenectomy, may temporarily help in the acute illness phase.¹⁰¹ Early intervention by the ophthalmology department is important to preserve vision.

Waardenburg syndrome

Key points

- Heterochromic irides and dystopia canthorum are classic eye findings of Waardenburg syndrome**
- Ophthalmology should be involved early on if Waardenburg syndrome is suspected**

Waardenburg syndrome is a rare genetic disorder accounting for 2% to 5% of congenital deafness. It is caused by a mutation in the PAX3, MITF, endothelin-3 (EDN3), SOX10, EDNRB, MITF, PSX3, or SNAI2 genes (Table VIII).^{95,102,103} It affects neural crest cells and includes 4 subtypes, each with a unique corresponding gene mutation and a predilection for various physical manifestations.^{103,104} Classically, WS presents with a congenital white forelock similar to that seen in piebaldism, lateral displacement of the medial canthi (dystopia canthorum), a hypertrophic nasal root, deafness, and partial or total heterochromia of the iris.¹⁰⁴ Skin biopsy specimens reveal an absence of melanocytes.¹⁰⁴

Therapy. All patients require ophthalmologic referral with appropriate management. The irregular depigmented patches of WS patients can be treated cosmetically with topical pigmenting agents such as self-tanning products or with skin grafting.¹⁰⁴

Table VII. Types of oculocutaneous albinism*

OCA type	Genetic defect	Skin and other findings	Eye findings
1A	Absence of TYR	Pinkish-colored skin, white hair, and lack of freckles and nevi that does not change with age	Blue-grey irides, prominent red-reflex, poor visual acuity, photophobia, nystagmus, foveal hypoplasia, and strabismus
1B	Decreased activity of TYR	Depigmented skin and white hair at birth, can acquire a tan, freckles, and nevi with age. Hair becomes yellow and eventually light brown	Iris translucency and nystagmus
2	Defect in "p gene" resulting in decreased eumelanin	At birth, hair may be pigmented and skin can have pigmented birthmarks. Color of skin and eyes increases with age and may not be noticeable by adulthood	Blue eyes may become brown with age, nystagmus and photophobia is less severe, but visual acuity decreased
3—"Rufous OCA"	Defect in TRP-1	Mahogany brown skin with light brown-red hair, freckles, lower risk of solar damage. More common in the African population	Hazel eyes, only 10% with strabismus and nystagmus
4	Defect in MATP	Clinically indistinguishable from OCA 2. More common in the Japanese population	Clinically indistinguishable from OCA 2. Has largest decrease in visual acuity
HPS	TYR ⁺ : 8 known gene mutations (HPS1/HPS3)	Hypopigmentation that darkens with age, acanthosis nigricans-like hyperpigmentation, and blonde hair. Dysfunctional platelets with no dense granules, interstitial pulmonary fibrosis, or granulomatous colitis	Nystagmus and decreased visual acuity
Chediak–Higashi syndrome	LYST gene mutation	White-grey skin, pigmented nevi, and silver metallic hair. Big granules trapped in lymphocytes and platelets cause immunodeficiency and easy bruising; giant melanosomes	Grey-blue or brown eyes, nystagmus, photophobia, and decreased visual acuity

HPS, Hermansky–Pudlak syndrome; MATP, membrane-associated transporter protein; OCA, oculocutaneous albinism; TRP-1, tyrosinase-related protein-1; TYR, tyrosinase.

*All conditions listed are inherited in an autosomal recessive manner.

Disorders of keratinization

Congenital lamellar ichthyosis

Key points

- Ectropion is common in lamellar ichthyosis and can lead to corneal scarring
- Ophthalmologists are essential to early care of a patient born with lamellar ichthyosis

Lamellar ichthyosis is an autosomal recessive disorder of transglutaminase-1 that results in a colloid membrane at birth and lifelong thick, plate-like cutaneous scales.¹⁰⁵ These patients are at increased risk of developing cicatricial ectropion, or pulling of the eyelid away from the eye caused by eyelid scarring contraction, which also results in an increased risk of corneal perforation.¹⁰⁵ Therefore, patients should be referred to and closely

monitored by an ophthalmologist. Patients also have madarosis (missing eyelashes), conjunctivitis, eyelash retraction, and lagophthalmos (incomplete eyelid closure).¹⁰⁵

Therapy. The ocular manifestations can normally be treated conservatively with preservative-free artificial tears, petroleum ointment, and bandage contact lenses, but some cases require surgical correction of the ectropion with full-thickness skin grafts.^{105,106}

X-linked ichthyosis

Key point

- White, comma-shaped opacities are seen in X-linked ichthyosis, causing corneal abrasions and possible scarring

X-linked ichthyosis is an X-linked recessive disorder caused by a deficiency of steroid sulfatase,

Table VIII. Types of Waardenburg syndrome

WS type	Inheritance type	Genetic mutation	Clinical findings
I	Autosomal dominant	PAX3	Piebald-like hypopigmented patches, heterochromia irides, broad nasal root, dystopia canthorum, sensorineural deafness, and synophrys
II	Autosomal dominant	MITF	WS type I without dystopia canthorum and most likely to have sensorineural deafness
III	Autosomal dominant	PAX3	WS type I plus musculoskeletal abnormalities
IV	Autosomal recessive	EDN3 or SOX10	WS type I plus Hirschsprung's disease because EDN3 controls migration of the neural crest cells including those that migrate to the Auerbach plexus

WS, Waardenburg syndrome.

a microsomal enzyme responsible for the desulfation of cholesterol sulfate.¹⁰⁷ The skin of XLI patients features mild scaling at birth, then develops prominent brownish polygonal adherent scales.¹⁰⁸ Between 10% and 50% of XLI patients have fine, white, comma-shaped opacities in their Descemet membrane (ie, the basement membrane between the posterior corneal stroma and endothelium), which do not affect visual acuity but can lead to recurrent corneal abrasions, scarring, and blindness.¹⁰⁸

In addition to the affected patients, up to 25% of all female carriers have these corneal opacities, which is the only physical finding to indicate their carrier status.^{107,108} Most patients fail to progress during pregnancy because of the inability of the placenta to convert dehydroepiandrosterone to estrogen, frequently necessitating birth by caesarean section. Patients with family history of XLI should consider prenatal screening with fluorescent in situ hybridization of the steroid sulfatase gene.⁹³ Another extracutaneous manifestation is cryptorchidism and resultant increased risk of testicular germ cell tumors.¹⁰⁸ Obstetricians and geneticists can help with family planning.

Therapy. Ophthalmology referral is only indicated if patients become symptomatic with eye pain and a foreign body–like sensation indicating a corneal abrasion. Prophylactic measures to prevent corneal abrasion include lubricating eye drops or ointments and avoidance of any eye rubbing.

Keratitis-ichthyosis-deafness syndrome

Key points

- Children with keratitis-ichthyosis-deafness syndrome have progressive keratitis, photophobia, dry eyes, and are at high risk for scarring visual impairment
- Referral to the ophthalmology and otolaryngology departments are appropriate

Keratitis-ichthyosis-deafness syndrome is a rare autosomal dominant or recessive disease characterized

by progressive vascularizing keratitis, dystrophic nails, malformed teeth, sensorineural hearing impairment, and stippled palmoplantar keratoderma.⁵⁷ It is caused by a missense mutation of the GJB2 gene responsible for the connexin-26 protein that allows for intercellular communication in the epidermis and cochlea.¹⁰⁹ Ocular findings consist of photophobia, dry eyes, and neovascularization of the cornea, which can lead to scarring and blindness. Patients also have recurrent corneal erosions, meibomitis, severe dry eyes, and corneal leucomae (white opacities).¹⁰⁹

Therapy. Eye disease has variable improvement with lubricating and antiinflammatory agents. If keratitis-ichthyosis-deafness syndrome is suspected, ophthalmology and otolaryngology referrals are necessary.

Ichthyosis follicularis alopecia and photophobia

Key points

- Ichthyosis follicularis alopecia and photophobia is a rare X-linked syndrome with alopecia universalis, seizures, intellectual impairment, short stature, and photophobia
- Ophthalmologists are central to the ongoing care of patients with ichthyosis follicularis alopecia and photophobia

Ichthyosis follicularis alopecia and photophobia (IFAP) is a rare X-linked recessive disorder of the MBTPS2 gene, which is responsible for cholesterol homeostasis. As of August 2013, only 43 cases have been reported.¹⁰⁹⁻¹¹² Ichthyosis follicularis alopecia and photophobia presents at birth with total body alopecia, seizures, decreased intellect, short stature, and photophobia.¹¹⁰ Cutaneous findings include noninflammatory spiny follicular projections, psoriasisiform plaques, atopic dermatitis with associated angular cheilitis, dystrophic nails, and hypohydrosis.¹¹⁰ Photophobia is a key feature and results from corneal ulceration that can progress to scarring and permanent blindness. Patients also suffer from cataracts, chronic tearing, nystagmus, astigmatism,

myopia, and atopic keratoconjunctival inflammation. Immediate ophthalmologic referral is imperative because of the numerous ocular findings. Other findings of IFAP include dysmorphic facial features, intestinal abnormalities, inguinal hernias, and cardiac and vertebral abnormalities. Diagnosis is made clinically with confirmation by genetic identification of the MBTPS2 gene.¹¹⁰

Therapy. Cutaneous manifestations can be treated with keratolytics, emollients, and urea lotions, with some patients responding to acitretin.¹¹⁰ Ocular treatment of IFAP requires intense lubrication of the ocular surface to minimize corneal scarring.^{57,110}

Refsum syndrome

Key point

- Refsum syndrome causes retinitis pigmentosa, a cause of night blindness, and can improve with dietary restriction of phytanic acid

Refsum syndrome is an autosomal recessive disease with ichthyosis caused by a mutation in the PAHX or PEX7 genes. The PAHX mutation results in an accumulation of phytanic acid in the serum and the PEX7 mutation results in a deficiency in multiple peroxisomal enzymes. This leads to multi-organ dysfunction, including cutaneous ichthyosis, cerebellar ataxia, sensorineural deafness, and arrhythmias with heart block. Retinitis pigmentosa with salt and pepper retinal pigment is characteristic for the disease and can result in night blindness; therefore, ophthalmologic referral is essential.

Therapy. Refsum syndrome is one of the reversible retinitis pigmentosa syndromes; treatment includes dietary restriction of phytanic acid, which can prevent disease progression when initiated early.¹¹³

Richner–Hanhart syndrome

Key point

- Dietary restriction of tyrosine and phenylalanine may prevent the devastating keratitis, photophobia, and blindness seen in patients with Richner–Hanhart syndrome

Richner–Hanhart syndrome (tyrosinemia type II) is a palmoplantar keratoderma caused by an autosomal recessive mutation in the tyrosine aminotransferase gene, resulting in deficiency of the hepatic enzyme and an accumulation of tyrosine in all tissues.¹¹³ Tyrosine crystals also accumulate in the corneal epithelium, inducing an inflammatory reaction that results in severe keratitis with photophobia, corneal ulceration, neovascularization, and eventual blindness. Eye symptoms typically present before

the cutaneous findings of sharply demarcated, painful, and erosive palmoplantar keratoderma.⁹³

Therapy. Ophthalmologic evaluation is imperative in the early diagnosis of Richner–Hanhart syndrome to prevent blindness. While there are several case reports of alternative therapies, mainstay treatment is dietary restriction of tyrosine and phenylalanine.¹¹³

Neoplasm associations

Basal cell nevus syndrome

Key points

- Basal cell nevus syndrome is caused by a PTCH1 mutation resulting in upregulation of pro-carcinogenic target genes and basal cell carcinoma formation
- Twenty-six percent of basal cell nevus syndrome patients have associated ocular abnormalities, including cataracts, hamartoma of the retina, and nystagmus
- Targeted therapies like vismedogib have decreased the basal cell carcinoma tumor burden in basal cell nevus syndrome patients

Approximately 1 in 56,000 people have basal cell nevus syndrome (BCNS), and the disease affects men and women equally.^{114,115} BCNS is an autosomal dominant disorder in which the patched (PTCH1) tumor suppressor gene, is mutated resulting in the absence of the patched homolog 1 (PTCH1) transmembrane protein receptor.¹¹⁵ Normally, PTCH1 inhibits smoothened, a G protein–couple receptor. The lack of PTCH1 results in constitutively active smoothened, which constantly activates GLI1 and GLI2, resulting in the upregulation of procarcinogenic target genes and basal cell carcinoma (BCC) formation. In addition to the multiple BCCs, BCNS patients present with other neoplasms, including medulloblastoma, ovarian and cardiac fibromas, and fetal type rhabdomyomas.

Twenty-six percent of affected patients with BCNS have associated ocular abnormalities, including glaucoma, cataracts and periocular BCCs.¹¹⁴ Other manifestations of BCNS include brain calcifications, palmoplantar pits, odontogenic jaw cysts, bifid rib, macrocephaly, and skeletal abnormalities.¹¹⁶

Therapy. Education, photoprotection, chemoprevention, and early treatment are essential for patients with BCNS. Vismodegib is an oral smoothened inhibitor and has been shown to decrease the rate of new BCCs after 8 months of therapy. In clinical trials, vismedogib decreased the size of BCCs by 65%, achieved a 30% response rate for metastatic BCCs, and achieved a 43% response by locally advanced

BCCs. However, 54% of patients in clinical trials discontinued therapy because of adverse events, the most common of which were muscle cramps, dysgesia, and alopecia. All of these resolved after discontinuation of therapy.^{117,118} New chemoprevention medications, including capecitabine, a 5-fluorouracil prodrug, are currently under evaluation for the treatment of squamous cell carcinoma, BCC, and actinic keratoses.¹¹⁹

Xeroderma pigmentosum

Key points

- **Xeroderma pigmentosum results from a genetic mutation leading to damage of the nucleotide excision repair pathway, and impairment of the cell's ability to repair DNA**
- **Ocular manifestations include eyelid tumors, corneal opacification, exposure keratitis, and photophobia**
- **Patients require aggressive photoprotection on a daily basis, including ocular protection with broad-spectrum sunglasses**

Xeroderma pigmentosum (XP) occurs in 1 per 1,000,000 people worldwide. It is caused by an autosomal recessive mutation in the nucleotide excision repair pathway that impairs the cell's ability to repair DNA. While there are 8 different gene mutations associated with XP, 50% of XP patients have XPA or XPC mutations.

Patients with XP develop ephelides and solar lentigines at 1 to 2 years of age. Actinic damage rapidly ensues with nonmelanoma skin cancer subsequently before 5 years of age (Fig 10). Patients are also at a 2,000-fold increased risk for melanoma compared to the general population. These malignancies can also develop on the oral mucosa, especially the tip of the tongue, as well as the eyelid and conjunctiva. Ocular neoplasms occur in 11% of patients, most frequently at the limbus (Fig 1).¹²⁰ Poikiloderma and photoaging are also seen much earlier in these patients.

More than 40% of XP patients have ocular findings, including eyelid atrophy and tumors, corneal sicca and opacification, exposure keratitis, pterygium, photophobia, and chronic conjunctival injection.¹²¹ Patients frequently complain of discomfort and visual disturbances. It is therefore important to examine the eyelids, conjunctiva, cornea, and iris of all XP patients and refer the patient to an ophthalmologist for full ophthalmologic work-up, because a loss of vision is likely if the ocular abnormalities are not detected early.^{121,122}

Therapy. Comprehensive patient education is essential for the treatment of XP, with a strong emphasis on aggressive photoprotection and full



Fig 10. Xeroderma pigmentosum.

Table IX. Differential diagnosis of angioid streaks

Pseudoxanthoma elasticum
Paget disease of bone
Ehlers–Danlos
Sickle cell anemia
Idiopathic thrombocytopenic purpura
Cutis laxa
Cowden disease
Osteogenesis imperfecta
Lead poisoning
Acrogyria

ocular protection with broad-spectrum sunglasses. Vismodegib, an oral hedgehog signaling pathway antagonist, is indicated for advanced BCCs. It is commonly used in patients with BCNS and may have a role in preventing advancement of the BCCs in XP patients.

Miscellaneous

Pseudoxanthoma elasticum

Key point

- **Angioid streaks, seen in pseudoxanthoma elasticum and other diseases, are caused by breaks in the Bruch membrane in the retina with resultant central loss of vision**

Pseudoxanthoma elasticum (PXE) is an autosomal recessive connective tissue disorder that is caused by mutation of the ABCC6 gene on chromosome 16. This results in an abnormal or absent MRP6 protein (an ABC-cassette efflux pump expressed in the liver and kidneys). Without this pump, various toxins accumulate in dermal fibroblast cells, causing an increased turnover of elastin and altered glycosaminoglycan metabolism.¹²³ PXE presents around 13 years of age with soft yellowish papules in a reticular pattern along the lateral neck and flexor surfaces creating a “cobblestone” appearance.^{124,125} The eye first shows pigment irregularities with peau d'orange retinal changes and later develops angioid streaks around the optic disc.¹²⁴ Differential diagnosis of angioid streaks are shown in Table IX. The angioid streaks represent breaks in the Bruch membrane



Fig 11. Pseudoxanthoma elasticum. Angiod streak of the right eye. (Photograph courtesy of Robert Wang, MD.)

along the posterior retina and can lead to neovascularization of the retina, retinal hemorrhage, scarring, and eventually loss of central vision (Fig 11).^{124,125} Therefore, all PXE patients must be referred to an ophthalmologist to reduce visual loss.

Cardiovascular changes include early atherosclerosis caused by elastic lamina damage with resulting softening and disappearance of peripheral pulse, claudication, angina pectoris, and rarely myocardial infarction or stroke indicating a cardiology consultation.¹²⁵

Therapy. Treatment of ocular choroidal neovascularization includes laser photocoagulation, surgery, photodynamic therapy, and intravitreous antiangiogenic agents.¹²⁴

Fabry disease

Key point

- **A whorled corneal opacity, “cornea verticillata,” is pathognomonic for Fabry disease and is seen in 80% of patients**

Fabry disease is caused by an X-linked recessive mutation in the alfa-galactosidase A gene causing accumulation of glycosphingolipids in lysosomes and multiorgan disease, including both cutaneous and ocular manifestations.^{15,126} The skin findings of Fabry disease include dry mouth, hypohydrosis, and angiokeratomas (dark red to blue black papules [<4 mm] that do not blanch and appear predominately in a bathing trunk distribution between the umbilicus and thighs).^{15,126} The pathognomonic eye change is “cornea verticillata,” or a whorled corneal opacity seen in 80% of Fabry patients.¹²⁶ These opacities are caused by glycosphingolipid deposits in the corneal epithelium that appear as fine grey-yellow lines that originate centrally and arch out radially. The majority of Fabry patients have vascular changes in the eye, such as venous

aneurysmal sacculations, conjunctival vascular abnormalities, and tortuous retinal vessels necessitating early ophthalmologic referral in any patient with suspected Fabry disease.¹²⁶

The most devastating findings of Fabry disease are internal organ dysfunctions, including left ventricular hypertrophy, arrhythmias, chronic kidney disease, ischemic stroke, and cerebral small vessel disease.¹²⁶ As a result, patients do not typically survive past 40 or 50 years of age.

In addition to ophthalmologic findings, the diagnosis can be made by measuring alfa-galactosidase A activity with a leukocyte assay.¹²⁷

Therapy. Early referral and proper communication among a cardiologist, nephrologist, neurologist, ophthalmologist, and dermatologist are necessary for the optimal management of patients with Fabry disease.¹²⁶

CONCLUSION

A multitude of oculocutaneous disease processes exist either in isolation or as part of more widespread systemic disease. It is essential that dermatologists have an understanding of the disorders—especially those with devastating sequelae, such as blindness. Dermatologists must play a key role in screening for these ocular issues and referring patients to ophthalmologists whenever necessary. Part II of this continuing medical education article reviews neoplastic and drug-induced oculocutaneous diseases.

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The spectrum of oculocutaneous disease

Part II. Neoplastic and drug-related causes of oculocutaneous disease

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Learning Objectives

After completing this learning activity, participants should be able to identify ocular symptoms associated with neoplastic and drug-related dermatologic disorders; recognize and differentiate the cutaneous manifestations of several ocular disorders; and order appropriate tasks and initiate timely referral to ophthalmologists and other subspecialists for early diagnosis, surveillance, and treatment of ocular disease.

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There are a multitude of diseases that commonly affect both the skin and the eye. Part II of this 2-part series reviews the oculocutaneous manifestations of neoplasms, both benign and malignant, and adverse drug reactions affecting the skin and the eye. Though rare, a number of neoplasms that primarily involve the skin, such as melanoma and basal cell carcinoma, can metastasize to the eye, leading to permanent damage if not properly treated. In addition, periocular neoplasms can irritate the conjunctiva and lid, reducing a patient's ability to see clearly. Neoplastic diseases, such as xeroderma pigmentosum, Sturge–Weber syndrome, and multiple myeloma, can also lead to permanent changes in the eye if not discovered and managed promptly. Furthermore, there are a multitude of drugs, including those commonly used by dermatologists, which can result in permanent damage to the eye. With proper knowledge of the ocular manifestations and treatment recommendations described in this 2-part series, dermatologists with the assistance of their ophthalmology colleagues can help avoid the complications, including permanent blindness, associated with infectious, inflammatory, genetic, neoplastic, and drug-related conditions. (J Am Acad Dermatol 2014;70:821.e1-19.)

Key words: basal cell nevus syndrome; cutaneous T-cell lymphoma; drug reactions; EGFR; inhibitormultiple myeloma; oculocutaneous; periocular neoplasm; PHACES; Stevens-Johnson Syndrome; Sturge Weber Syndrome; toxic epidermal necrolysis; xeroderma pigmentosum.

INTRODUCTION

There are multiple diseases that concomitantly affect the ocular and cutaneous organ systems as a result of their mutual ectodermal origin. Part I of this two-part CME article reviewed the full spectrum of infectious, inflammatory, and genetic diseases common to both these organs. Part II focuses on neoplastic and drug-related oculocutaneous manifestations with recommendations for appropriate diagnosis and treatment by dermatologists and referral as necessary to our ophthalmology colleagues. A summary of ocular manifestations can be found in [Tables I and II](#).

NEOPLASTIC

Benign

Squamous cell papilloma of the eyelid

Key points

- **Squamous cell papillomas are associated with human papillomavirus types 6 and 11**
- **Large periorbital lesions can induce astigmatism and are cosmetically unappealing**
- **Treatment involves intralesional interferon-alfa or surgical excision**

A squamous cell papilloma, also known as infectious conjunctival papilloma, is one of the most

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Table I. Summary of eye findings in malignant and benign neoplasms

Neoplastic	Ocular manifestations
Benign	
Squamous cell papilloma of the eyelid	Blurred or decreased vision and astigmatism
Sturge—Weber syndrome	Choroid malformation, glaucoma with secondary buphthalmos, and vision loss
PHACES syndrome	Microphthalmia, strabismus, and morning glory deformity
Malignant	
Cutaneous T-cell Lymphoma	Uveitis, chronic vitritis, and retinal vasculitis
Multiple myeloma	Proptosis, diplopia, ptosis, and orbital edema
Basal cell carcinoma	Invasion of the bulbar conjunctiva, displacement of the globe, immobility of eye, and orbital bone destruction
Basal cell nevus syndrome	Strabismus, cataracts, nystagmus, cysts, and periocular basal cell carcinomas
Periocular squamous cell carcinoma	Pruritus, dry eye, globe displacement, diplopia, altered sensation around the eye, and loss of vision
Periocular sebaceous carcinoma	Discrete, hard, immobile nodule with a yellowish hue or a thickened lid with loss of eyelashes
Melanoma	Blurred vision, eye pain, exophthalmos, diplopia, and floaters
Xeroderma pigmentosum	Eyelid atrophy, corneal sicca and opacification, and pterygium

PHACES, Posterior fossa brain malformations, large facial hemangioma, arterial anomalies, cardiac anomalies and aortic coarctation, eye abnormalities, sternal clefting and/or supraumbilical raphe.

Table II. Summary of medication-induced eye findings

Medication-induced manifestations	Ocular manifestations
Patients with SJS and TEN	Conjunctivitis, corneal erosions, and symblepharon
Systemic retinoids	Dry eye, corneal opacities, cataracts, and night and color blindness
Tumor necrosis factor—alfa inhibitors	Endophthalmitis, uveitis, optic neuritis, and ciliary injection
Topical glucocorticosteroids	Irritation, glaucoma, cataracts, ocular hypertension, infection, and skin atrophy
Interferon-alfa	Blurred vision caused by cotton wool spots, retinal hemorrhage, and retinal microaneurysms
Epidermal growth factor receptor inhibitor	Trichomegaly, dry eye, and periorbital erythema
Antimalarial drugs	Cataracts, corneal deposits, and bull's eye retinopathy
Cyclosporine	Trichomegaly, visual hallucinations, and cerebral blindness

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

common benign neoplasms of the eyelid and conjunctiva, making up 26% of benign eyelid tumors.¹ Squamous papillomas are associated with human papillomavirus types 6 and 11 and typically occur in children and young adults. The lesion presents on the lid margin, predominantly near the medial canthus, and can be sessile or pedunculated. In addition, these viral papillomas can present in the conjunctival fornices. The patient's vision is usually unaffected. If large, however, the lesion can induce astigmatism, necessitating removal. The characteristic presence of hyperkeratosis, papillomatosis, and finger-like projections of the epidermis are seen histologically.² If a patient presents with a squamous cell papilloma of the eyelid and is complaining of changes in vision or cosmetic issues, then ophthalmologic referral should be considered.³

Therapy. Conjunctival papillomas are often treated with cryotherapy or excisional biopsy. Recent studies have also shown that intralesional interferon-alfa may be used to treat squamous cell papillomas of the eyelid to prevent potential cosmetic problems associated with surgical excision, such as eyelid thinning and eyelash loss.⁴

Sturge—Weber syndrome

Key points

- Sturge—Weber syndrome is a congenital neurologic condition caused by a sporadic mutation that leads to defective morphogenesis
- The risk of ocular involvement is increased in those with large bilateral facial capillary malformations
- Ocular manifestations include choroid malformation, glaucoma with secondary

buphthalmos, and visual loss necessitating immediate timely referral to an ophthalmologist

Sturge–Weber syndrome (SWS) is caused by a sporadic mutation that results in defective morphogenesis within the cephalic neural crest. It was recently discovered that a large majority of SWS patients have a somatic activating mutation in GNAQ, a gene that encodes $G\alpha_q$, a G-protein alfa subunit, which facilitates signals between G-protein–coupled receptors, including endothelin and downstream effectors like extracellular signal-regulated kinase.⁵ These patients are born with a capillary malformation (port wine stain) in the distribution of the trigeminal nerve (ie, cranial nerve V, branches V₁, V₂, and V₃). The port wine stain is well demarcated and erythematous to violaceous with additional darkening as the patient ages.⁶ Seizures frequently develop in these patients at 1 to 2 years of age. Involvement is predominantly unilateral, involving the V₂ and V₃ distributions. Because of the overlying capillary malformation, there is progressive soft tissue and skeletal hypertrophy. Within the central nervous system (CNS) on the ipsilateral side, there are capillary, venous, and arteriovenous malformations within the leptomeninges together with “tram track” calcifications in the temporal and occipital cortex. The CNS findings are best diagnosed with magnetic resonance imaging scans with gadolinium.⁷ The eyes are affected in 32% to 65% of the patients, with the risk increasing in patients with large, bilateral facial vascular malformations. These ocular manifestations include choroid malformation, glaucoma with secondary buphthalmos (enlargement of the eyeball), and visual loss necessitating timely referral to an ophthalmologist. In these patients, vision loss is caused by retinal detachment because of diffuse choroidal hemangiomas. Currently, treatment for this condition consists of photocoagulation, subretinal fluid drainage, and radiation therapy. A recent case report, however, has shown success in treating diffuse choroidal hemangiomas with secondary retinal detachments with oral propranolol.⁸

PHACES syndrome**Key points**

- PHACES syndrome is a rare congenital disorder consisting of a multitude of findings that always include a facial hemangioma
- Common ocular findings include morning glory disc anomaly, amblyopia, and microphthalmia

• Propranolol successfully treats the hemangiomas seen with PHACES

Posterior fossa brain malformations, large facial hemangioma, arterial anomalies, cardiac anomalies and aortic coarctation, eye abnormalities, sternal clefting and/or supraumbilical raphe (PHACES) syndrome is a rare congenital constellation of findings including the presence of a facial hemangioma. There is an increased prevalence reported in females (9:1), Hispanics, and whites.⁹ Typically, PHACES patients will present with symptoms before 12 months of age.¹⁰

Patients with PHACES syndrome have a 24% likelihood of ocular involvement. Facial involvement of the temporal or periorbital area increases the incidence of ipsilateral ocular deformities. Such ocular manifestations include morning glory disc anomaly, amblyopia, microphthalmia, and the items listed in Table III.^{11,12} Morning glory disc anomaly is a congenital malformation in which there is ectasia of the posterior pole of the fundus that involves the optic nerve. In 90% of patients with this anomaly, visual acuity is 20/200 or worse. Exudative retinal detachment occurs in 30% of these patients.¹³

Therapy. Oral corticosteroids have been used as first-line therapy for treating PHACES for decades. Recently, however, corticosteroids have been used solely as short-term treatment, because propranolol, vincristine, and interferon have all been shown to successfully treat PHACES.¹⁴ Propranolol is now considered first-line therapy for many cases of PHACES as it is for infantile hemangiomas. It reduces the size of facial and orbital hemangiomas while also improving strabismus and amblyopia.^{9,14,15} In addition, cutaneous telangiectasias will typically resolve with the use of propranolol. If not, the cutaneous vascular lesions can be lightened with a pulsed dye laser.

Care must be taken when considering the initiation of propranolol in PHACES syndrome patients, because there is theoretical concern for potential cerebrovascular hypoperfusion if the patient has existing cerebrovascular abnormalities. However, in 2 studies of 39 patients, propranolol has been shown to be safe when administered to PHACES syndrome patients.^{12,16} Therefore, a magnetic resonance angiography scan of the cerebrovascular system is recommended before the initiation of propranolol along with management in close conjunction with a neurologist.¹⁷

Propranolol, however, does not treat the ocular abnormalities. Therefore, patients presenting with facial hemangiomas, especially when periocular and

Table III. PHACES syndrome: Common ocular findings

Amblyopia
Cataracts
Colobomas
Glaucoma
Micropthalmia
Morning glory disc anomaly
Optic nerve hypoplasia
Retinal hemangiomas
Strabismus

PHACES, Posterior fossa brain malformations, large facial hemangioma, arterial anomalies, cardiac anomalies and aortic coarctation, eye abnormalities, sternal clefting and/or supraumbilical raphe.

intraorbital in nature, in addition to those carrying the diagnosis of PHACES should seek early ophthalmologic evaluation.

Malignant

Cutaneous T-cell lymphoma

Key points

- The most common cutaneous T-cell lymphoma subtypes are Sézary syndrome and mycosis fungoides
- Advanced mycosis fungoides can infiltrate or metastasize to the eye, causing blepharitis, cicatricial ectropion, meibomianitis, chalazia, and madarosis. The most common ocular manifestation of Sézary syndrome is blepharitis
- Stage IV mycosis fungoides is typically treated with systemic chemotherapy. Extracorporeal photopheresis alone or in combination with chemotherapy are the suggested treatments of choice for Sézary syndrome

The incidence of primary cutaneous lymphoma is 0.7 per 100,000 people per year.¹⁸ Seventy-five percent to 80% of these cases are cutaneous T-cell lymphomas (CTCLs), with the remainder classified as cutaneous B-cell lymphomas (CBCL).¹⁹ According to the World Health Organization classification, subtypes of CTCL include mycosis fungoides and its variants, Sézary syndrome, primary cutaneous CD30⁺ lymphoproliferative disorders, subcutaneous panniculitis-like T-cell lymphoma, extranodal natural killer/T-cell lymphoma (nasal type), and primary cutaneous peripheral T-cell lymphoma not otherwise specified. Staging of these lymphomas involves evaluations of the skin, lymph nodes, viscera, and blood. Sézary syndrome and mycosis fungoides are the 2 most common forms of CTCL. Sézary syndrome



Fig 1. Blepharitis in a patient with Sézary syndrome.

is a triad of erythroderma, generalized lymphadenopathy, and neoplastic T cells (Sézary cells) in the skin, lymph nodes, and peripheral blood.²⁰ The criteria for diagnosis include an absolute Sézary cell count of at least 1000 cells/mm³, a ratio of CD4:CD8 T cells >10, or a chromosomally abnormal T cell clone.²⁰ Patients experience intense pruritus, marked exfoliative dermatitis with palmoplantar hyperkeratosis, edema, and lichenification. Ocular manifestations relate predominantly to the associated blepharitis (Fig 1).

Mycosis fungoides, a mature T-cell cutaneous lymphoma involving the skin, lymph nodes, peripheral blood, and viscera, may also involve the eye in 30% of patients. This typically presents as tumors or infiltration of the eyelid, resulting in cicatricial ectropion, meibomianitis, chalazia, and madarosis.^{21,22}

Rarely, these and other forms of CTCL can metastasize intraocularly via hematogenous spread to the uvea, retina, and vitreous humor.²³ Any patient diagnosed with advanced or metastatic CTCL needs to be questioned regarding changes in vision including floaters, scotomas, or blurred vision, because these findings may indicate uveitis, chronic vitritis, and retinal vasculitis, respectively. If metastasis is suspected, then referral to an ophthalmologist for evaluation, biopsy, and molecular and immunophenotypic analysis is indicated.^{18,23,24}

Therapy. Extracorporeal photopheresis (ECP) alone or in combination with chemotherapy are the suggested treatments of choice for Sézary syndrome.²⁰ A number of treatments are used in the treatment of stage IV mycosis fungoides, such as ECP, localized radiotherapy, and systemic chemotherapy, including cyclophosphamide, hydroxydaunorubicin, oncovin, and prednisone (CHOP) chemotherapy, histone deacetylase inhibitors, and bexarotene.²⁵ Ocular radiation has also been shown to improve vision and reverse a large majority of intraocular metastases.¹⁸

Multiple myeloma

Key points

- Thirty-five percent of patients with multiple myeloma develop ocular manifestations
- Proptosis, decreased vision, diplopia, swelling, and ptosis are the most common symptoms of ocular and orbital plasmacytomas

- Treatment for ocular plasmacytomas typically involves local radiation or a combination of surgery and chemotherapy**

Multiple myeloma, the most common plasma cell tumor, affects 5 to 6 per 100,000 people each year in the United States.²⁶ It occurs mainly in those between 40 and 70 years of age.²⁷ Cutaneous manifestations have been found in up to 20% of patients with multiple myeloma. The most common dermatologic manifestations are plasmacytomas, nonthrombocytopenic purpura, amyloidosis, pyoderma gangrenosum, and leukocytoclastic vasculitis.²⁷ Follicular hyperkeratosis and necrobiotic xanthogranuloma have also been reported.^{27,28}

Thirty-five percent of patients with multiple myeloma will develop ocular manifestations. On average, symptoms of ocular disease present 17.6 months after initial diagnosis.²⁶ While proptosis, decreased vision, diplopia, swelling, and ptosis are the most common symptoms of ocular and orbital plasmacytomas, it is important to note that multiple myeloma can affect almost all structures within the eye. Therefore, there are a wide variety of ocular findings, including choroidal effusion, retinal capillary microaneurysms, extraocular muscle paresis, and corneal deposition.²⁶

Ocular spread of multiple myeloma can lead to pain and changes of vision, stressing the importance of an annual eye examination in these patients to prevent any permanent changes. The ophthalmologist may order a computed tomography scan with coronal imaging or high-frequency ophthalmic ultrasonography to help determine the extent of disease within the eye, because these methods allow for the best visualization of ocular plasmacytomas. If left uncontrolled, symptoms will worsen and can progress to blindness. If an ocular plasmacytoma is found, follow-up with a hematologist oncologist or an ocular oncologist needs strong consideration.

Therapy. Treatment for ocular plasmacytomas typically involves local radiation or a combination of surgery and chemotherapy. For solitary lesions, local excision is possible, with enucleation rarely necessary.²⁶

Basal cell carcinoma

Key points

- Basal cell carcinomas comprise 80% to 95% of lid and medial canthus malignancies**
- Orbital invasion occurs in 5% of patients and may present as invasion of the bulbar conjunctiva, displacement of the globe, immobility of the eye, or without any signs or symptoms**

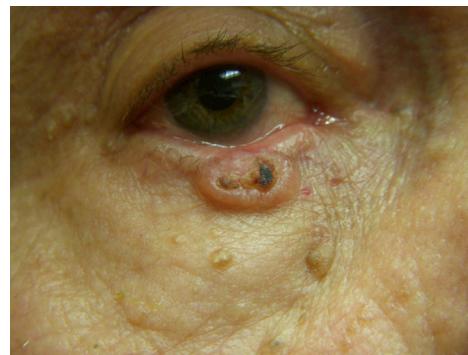


Fig 2. Basal cell carcinoma of the right lower eyelid.

- Treatment options for basal cell carcinoma metastatic to the eye include exenteration with or without radiotherapy, excision or Mohs micrographic surgery with or without radiotherapy, or radiotherapy as monotherapy**

Basal cell carcinoma (BCC), a slow growing tumor with a very low metastatic rate, is the most common skin malignancy. Though it does not commonly present periocularly, BCC does comprise 80% to 95% of lid and medial canthus malignancies (Fig 2). Periocular BCC infiltrates the eye in <5% of patients; when it does, it most commonly invades the orbit periosteally.²⁹ The mean duration from initial diagnosis of BCC to orbital invasions is 8.5 years. The most common location of periocular BCC is the lower lid, but it can also present on the medial canthus where it is most likely to invade the orbit. While the reasoning behind this remains unknown, it has been postulated that it is associated with difficulty in complete excision of the BCC from the canthus as opposed to the more routine excision on the lower lid. The histologic subtype also affects the likelihood of intraorbital metastasis. The more aggressive morpheaform subtype is most likely to invade the orbit, whereas superficial and nodular rarely invade the eye. Perineural invasion occurs very rarely with BCC (<1% of patients). However, in patients with intraocular spread of BCC, the risk of perineural invasion increases markedly to 19.3%.²⁹

Patients with orbital invasion of a periocular BCC may present with invasion of the bulbar conjunctiva, displacement of the globe, immobility of the eye, or no signs or symptoms at all. Therefore, it is important to order the appropriate imaging on any patient presenting with high-risk periocular BCC because, if left untreated, BCC can invade the surrounding nerves, rectus muscles, lacrimal sac, ethmoid sinus, or cribriform plate.^{29,30}

High-risk periocular BCCs include recurrent periocular BCCs, those located at the medial canthus, and those with an infiltrative histologic subtype, including morpheaform and basosquamous.^{29,30} BCC can also invade the superior orbital fissure and spread to the dura, cavernous sinus, and cerebral tissue. Orbital bone destruction has also been observed.

Therapy. Treatment options for BCC metastatic to the eye include exenteration with or without radiotherapy, excision or Mohs micrographic surgery with or without radiotherapy, or radiotherapy as monotherapy. Treatment choice must be determined based on extent of orbital invasion, visual function, and the patient's overall health.²⁹

Basal cell nevus syndrome

Key points

- **Basal cell nevus syndrome is an autosomal disorder with a mutation in the *PTCH1* gene, located on chromosome 9, resulting in the upregulation of procarcinogenic target genes and basal cell carcinoma formation**
- **Twenty-six percent of affected patients with basal cell nevus syndrome have associated ocular abnormalities, including cataracts, hamartoma of the retina, and nystagmus**
- **Targeted therapies like vismodegib have decreased the basal cell carcinoma tumor burden in patients with basal cell nevus syndrome**
- **New chemoprevention medications, including capecitabine, a 5-fluorouracil prodrug, are under evaluation**

Approximately 1 in 56,000 people have basal cell nevus syndrome (BCNS), and it affects men and women equally.^{31,32} BCNS is an autosomal dominant disorder in which the patched (*PTCH1*) tumor suppressor gene, located on chromosome 9q22.3-q31, is mutated, resulting in no patched homolog 1 (*PTCH1*) transmembrane protein receptor.³² Normally, *PTCH1* inhibits smoothened, a G-protein–coupled receptor. The presence of sonic hedgehog protein allows smoothened to be released by *PTCH1* and activate glioma-associated oncogene homologs 1 and 2 (*GLI1* and *GLI2*). The lack of *PTCH1* results in constitutively active smoothened, which constantly activates *GLI1* and *GLI2*, resulting in the upregulation of procarcinogenic target genes and BCC formation. In addition to the multiple BCCs, BCNS patients present with other neoplasms, including medulloblastoma, ovarian and cardiac fibromas, and fetal type rhabdomyomas.

Twenty-six percent of affected patients with BCNS have associated ocular abnormalities, such as cataracts, nystagmus, coloboma of the uvea and iris, hamartoma of the retina, or cysts of the eyelid and conjunctiva.³¹ In patients experiencing symptoms suggestive of these manifestations—especially if cataracts or glaucoma are suspected, because these can lead to vision loss—consultation with an ophthalmologist should be considered.³¹ Other manifestations of BCNS include brain calcifications, palmoplantar pits, odontogenic jaw cysts, bifid rib, macrocephaly, and skeletal abnormalities.³³

Therapy. Education, photoprotection, chemoprevention, and early treatment are essential to the treatment of patients with BCNS. Vismodegib is a smoothened inhibitor and has been shown to decrease the rate of new BCCs and decrease the tumor burden of both locally advanced and metastatic disease. Despite vismodegib's high efficacy, it is often discontinued because of adverse events, the most common being muscle cramps, dysgesia, and alopecia, which resolve after discontinuation of therapy.^{34,35} New chemoprevention medications, including capecitabine, a 5-fluorouracil prodrug, are under evaluation.³⁶ Capecitabine has shown a decreased incidence of squamous cell carcinomas, BCCs, and actinic keratoses, with tolerable gastrointestinal side effects in a small study of organ transplant recipients.³⁶ In addition, chronic low-dose capecitabine has been shown to be safe and well tolerated in the gastrointestinal literature for the treatment of gastrointestinal carcinomas.³⁶

Periocular squamous cell carcinoma

Key points

- **Periocular squamous cell carcinomas most commonly present on the lower eyelid, but may also be found on upper lid and medial canthus**
- **Symptoms of perineural invasion of squamous cell carcinoma include tenderness of the lesion, altered sensation around the eye, upper lid ptosis, diplopia, globe displacement, proptosis, or reduced vision**
- **Surgical excision with Mohs micrographic surgery is necessary to prevent continued irritation, metastasis, and perineural invasion of the disease**

Periocular squamous cell carcinoma (SCC) comprises 5% to 10% of eyelid tumors and usually presents as a painless plaque-like or nodular lesion with scaling, rolled edges, fissuring, and ulceration. Less commonly, periocular SCCs present as a small erythematous patch, a large fungating mass, a

cutaneous horn, or a small nodular or papillomatous lesion.³⁷ A majority of periocular SCCs are found on the lower eyelid, and less frequently on the upper eyelid and medial canthus.³⁸ The differential diagnosis includes actinic keratosis, BCC, and blepharitis.³⁹ Therefore, obtaining a biopsy specimen of the lesion is important to confirm the diagnosis, especially because 3% to 5% of SCCs *in situ* progress into invasive carcinoma, and 10% to 25% of invasive periocular SCCs metastasize to regional lymph nodes, typically parotid and preauricular nodes or submandibular and submental nodes. Those that metastasize tend to be large (>2 cm) recurrent lesions.³⁸

Perineural invasion of periocular SCC can lead to invasion of the orbit, intracranial cavity, and periorbital structures via the trigeminal nerve, extraocular motor nerves, and facial nerve.³⁸ Symptoms include tenderness of the lesion, altered sensation around the eye, upper lid ptosis, diplopia, globe displacement, proptosis, or reduced vision. Paralysis of the eye and facial nerve palsy can result if left undiagnosed. Therefore, if perineural invasion is suspected, oculoplastic surgery referral must be given strong consideration. Imaging studies help with surgical planning and may show an ocular adnexal pseudocyst, which is characteristic of perineural spread.³⁸

Therapy. Once the diagnosis of SCC of the eyelid has been made, surgical excision with Mohs micrographic surgery is necessary to prevent continued irritation, metastasis, and perineural invasion of the disease. After margin clearance with Mohs micrographic surgery, the defect frequently requires careful reconstruction by oculoplastic surgeons. While studies have shown success with the use of topical 5-fluorouracil to treat early SCC *in situ* of the eyelid, surgical excision remains the treatment of choice.³⁹ Supraorbital nerve exenteration, either subtotal or complete, may be required if the SCC extends into the orbit. The supraorbital nerve is the most common site for perineural invasion among periocular SCCs.³⁸

Periocular sebaceous carcinoma

Key points

- **Periocular sebaceous gland carcinoma is the third most common malignant eyelid tumor, affecting mostly women between 60 and 70 years of age**
- **These tumors present as a hard, immobile mass or as eyelid thickening with loss of lashes, which at first glance may look inflammatory**
- **Treatment depends on the stage of disease at presentation and can include local excision,**

enucleation of the eye, radical neck dissection, radiation, or chemotherapy

Periocular sebaceous carcinoma arises from the meibomian glands, glands of Zies, or glands associated with the caruncle and accounts for 0.5% to 5% of all eyelid carcinomas in the United States. Therefore, it is the third most common malignancy of the eyelid, with the upper lid most frequently involved because of the increased number of meibomian glands. Sebaceous carcinoma does occur on the lower eyelid, medial canthus, and on the trunk and extremities.^{40,41} Sebaceous carcinomas in any location must prompt an evaluation for Muir–Torre syndrome, an autosomal dominant mutation in the MSH2 (most common), MLH1, MSH6, PMS2, and MLH3 mismatch repair genes.⁴² Muir–Torre syndrome is a variant of Lynch syndrome and includes 1 sebaceous neoplasm and a primary internal malignancy, most commonly gastrointestinal—although genitourinary, pancreatic, and hematologic malignancies also are associated.^{40,42,43} Periocular sebaceous carcinomas are most commonly found in women between 60 and 70 years of age, whereas nonperiocular sebaceous carcinomas are more common in elderly men.^{44,45}

Sebaceous carcinoma presents as a discrete, hard, immobile nodule with a yellowish hue, similar to a chalazion, or as a thickened lid with loss of eyelashes, similar to blepharoconjunctivitis. Because of its resemblance to benign inflammatory lesions, sebaceous carcinomas are often not diagnosed until metastasis has occurred.⁴⁰ Therefore, it is important to obtain a biopsy specimen of any chronic, benign-appearing lesions that have failed to respond to standard therapy. Histologically, sebaceous carcinoma features a pagetoid spread of clear cells with crenulated nuclei, which stain with epithelial membrane antigen and androgen receptors but not carcinoembryonic antigen or S100. However, epithelial membrane antigen stain can be lost in poorly differentiated sebaceous carcinomas. The lipids in the neoplastic sebocytes will stain with oil red O and Sudan black.

Metastasis occurs by continuous growth or lymphatic or hematogenous spread. Forty-one percent of patients with sebaceous gland carcinoma will have metastatic disease on presentation, with the most common sites being the orbit, preauricular and submandibular nodes, and the parotid gland.⁴¹ The 5-year survival rate of sebaceous carcinoma is 96%,⁴⁴ but the mortality of metastatic disease is 25%.⁴¹ Therefore, any patient with sebaceous carcinoma who complains of changes in vision or pain in the eye needs evaluation for metastatic disease. This could include an ophthalmologic referral.⁴¹

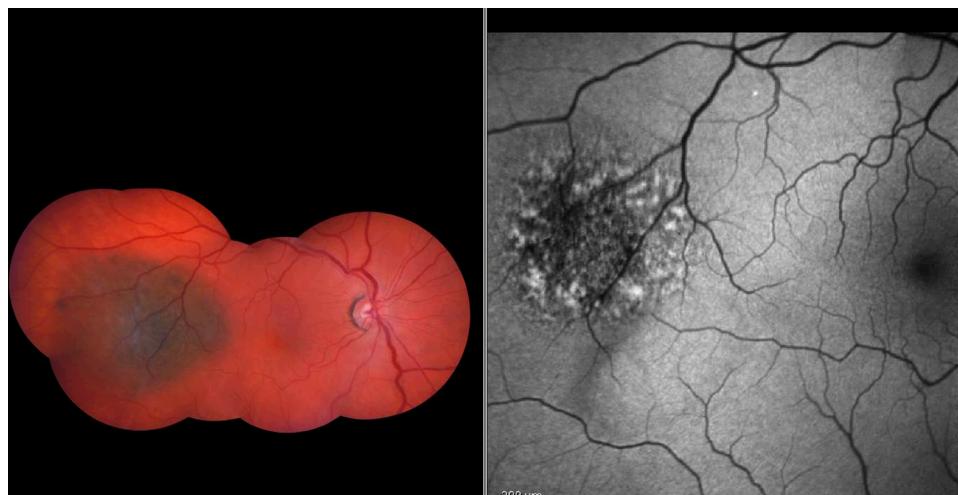


Fig 3. Melanoma montage revealing ocular melanoma of the right eye with classic lipofuscin pigment. Black and white fundus autofluorescent picture revealing lipofuscin indicative of ocular melanoma in the same patient. (Photograph courtesy of Robert Wang, MD.)

Therapy. Mohs micrographic surgery or standard excision with frozen section margin control are generally accepted as the treatment modalities of choice; however, there is no consensus in the literature. Surgical excision may include enucleation of the eye, depending on the extent of the tumor. Metastatic disease can be treated with excision and chemotherapy. Typically, sebaceous carcinoma is radioresistant and therefore is considered palliative and is only used in those who refuse or cannot undergo surgery.⁴³ Before surgical intervention, it is essential to examine the patient for spread into the conjunctiva, eye, eyelid, regional lymph nodes, and parotid gland. In addition, topical mitomycin C has been used to treat conjunctival invasion with some success.⁴⁶ Even after Mohs micrographic surgery or surgical resection, however, the recurrence rate of sebaceous carcinoma is 30%.⁴¹

Melanoma

Key points

- Primary intraocular melanoma is most commonly choroidal and is extremely rare, affecting fewer than 3000 North Americans each year
- Ocular metastasis can occur in patients with advanced melanoma
- Radioactive plaque, resection of the tumor, or enucleation of the eye can be effective for treating ocular melanoma

In the United States, 1 in 36 men and 1 in 52 women develop melanoma, with a higher prevalence seen in whites.⁴⁷ The World Health Organization states that there are 132,000 new

cases worldwide of melanoma each year. The Collaborative Ocular Melanoma Study by the National Eye Institute determined the most common primary tumor of the eye to be choroidal melanoma, making the choroid the most common location for primary ocular melanoma (Fig 3).⁴⁸ Primary intraocular melanoma is exceedingly rare, affecting <3000 North Americans each year. In addition, melanoma can involve the conjunctiva and the eyelid. While primary intraocular melanoma grows more slowly and is less aggressive than metastatic intraocular melanoma, the symptomatology and treatment of the 2 are the same.^{49,50} Therefore, all patients reporting vision changes, redness of the eye, or pain in the eye should visit an ophthalmologist promptly to avoid additional damage to the eye.⁵⁰

Ocular metastasis of melanoma is rare and only occurs in patients with advanced disease.⁵¹ The average interval between the diagnosis of primary cutaneous melanoma and intraocular metastasis is 3 years.⁴⁹ The most common location for metastasis is the posterior pole of the eye, namely the choroid, vitreous, retina, or ciliary body. Rarely, melanoma metastasizes to the iris or lens capsule.⁵² These intraocular tumors show little to no fluorescein leakage and do not show mature vascularization. They can be bilateral, diffuse, or multifocal.⁴⁹

Although intraocular metastasis is rare, a delay of diagnosis can result in loss of the eye. Therefore, patients with metastatic melanoma must be monitored for the development of intraocular disease. If a patient with cutaneous melanoma presents with symptoms of decreased vision, redness, pain in the eye, diplopia, floaters, or any other visual

problems, referral to an ophthalmologist should be actively considered.

Therapy. Radioactive plaque, resection of the tumor, or enucleation of the eye can be effective for treating ocular melanoma.⁴⁹ Enucleation of the eye is considered the primary treatment in patients with diffuse ocular melanoma or extraocular extension.⁵³

DRUG-RELATED

Stevens–Johnson syndrome and toxic epidermal necrolysis

Key points

- Stevens–Johnson syndrome and toxic epidermal necrolysis are drug reactions affecting both the skin and mucous membranes
- Ocular complications have been reported in 50% of patients suffering from Stevens–Johnson syndrome and toxic epidermal necrolysis. They include conjunctivitis, episcleritis, corneal erosions, symblepharon, corneal ulceration, and fornix foreshortening
- Treatment may include lubricating eye drops and early amniotic membrane transplantation over the entire ocular surface and eyelid margins

Both Stevens–Johnson syndrome (SJS) and toxic epidermal necrosis (TEN) are medical emergencies that affect the skin and mucous membranes. Drugs that can commonly lead to SJS and TEN include allopurinol, cephalosporins, corticosteroids, sulfonamides, and valproic acid amongst others. Symptoms of SJS or TEN usually begin days to weeks after initiating therapy with the causative drug.

When evaluating a patient with possible SJS or TEN, it is important to evaluate the eyes, skin, and mucosa. The cutaneous findings are listed in Table IV. Conjunctivitis, episcleritis, corneal erosions, symblepharon, corneal ulceration, and fornix foreshortening are ocular complications seen in 50% of patients suffering from SJS and TEN and are an essential part of the diagnostic criteria.⁵⁴ The high potential for ocular involvement warrants urgent ophthalmologic consultation in addition to the immediate identification and removal of the causative drug.

Therapy. Ocular treatment includes applying preservative-free lubricating eye drops and ointments as soon as possible.⁵⁵ The use of topical corticosteroids is controversial.⁵⁵ Early amniotic membrane transplantation over the entire ocular surface and eyelid margins has shown significant long-term benefit.⁵⁶ In addition, the ocular manifestations can

be managed surgically with symblepharon rings. Skin grafts may be indicated if eyelid structure is compromised. Despite treatment, the mortality rate is 1% to 5% for SJS and 25% to 30% for TEN.

Systemic retinoids

Key points

- Systemic retinoids frequently cause dryness of the eyes and photophobia
- Other ocular manifestations are blepharoconjunctivitis, and keratitis, corneal opacities, cataracts, night blindness, or loss of color vision
- Treatment of side effects involves the frequent use of moisturizing, preservative-free lubricating eye drops and bedtime ointments

The use of systemic retinoids is commonplace in dermatology for the treatment of psoriasis, acne, ichthyosis, and other inflammatory dermatoses. Mucocutaneous side effects are the most common adverse event, particularly with isotretinoin. Systemic retinoids commonly cause dryness of the eyes, which may result in discomfort, photophobia, blepharoconjunctivitis, and keratitis. These side effects are likely caused by significant drying related to atrophy of the meibomian glands and a reduction in the size of sebaceous glands.^{57,58} In addition, corneal opacities, cataracts, night blindness, and loss of color vision may be observed.⁵⁷ The exact cause of vision changes and cataracts is unknown, but vitamin A toxicity may be involved.⁵⁸ Lastly, some cases of premacular hemorrhage associated with retinoid use have been reported.⁵⁹

Patients experiencing ocular or cutaneous symptoms while taking systemic retinoids typically report them within a month of beginning therapy. The severity of the ocular side effects are often dose-dependent and therefore can be ameliorated by dose adjustment.⁵⁷ Patients initiated on retinoid therapy should be fully educated at the first visit with the appropriate use of artificial tears or emollients and screened for ocular symptoms at each subsequent visit.

Therapy. If early ocular side effects are observed, patients should avoid wearing contact lenses and again be advised to frequently use moisturizing, preservative-free lubricating eye drops and bedtime ointments. Reversible punctal occlusion with silicone punctal plugs typically leads to resolution of the side effects. In patients who experience symptoms outside of the typical dryness, including blurry vision, night blindness, color vision loss, glaucoma, cataracts, or retinal hemorrhage, retinoid therapy must be immediately discontinued and referral to an ophthalmologist should be considered.^{57,59}

Tumor necrosis factor–alfa inhibitors

Key points

- Ocular side effects include endogenous endophthalmitis, uveitis, and optic neuritis
- Ocular side effects of these drugs typically develop within 3 to 24 months after the initiation of anti–tumor necrosis factor–alfa therapy
- If ocular side effects occur, then the tumor necrosis factor–alfa inhibitor must be discontinued and immediate ophthalmologic consultation and referral to an ophthalmologist considered to minimize permanent vision changes

Tumor necrosis factor–alfa inhibitors (TNF- α inhibitors) are biologic agents that are commonly used to treat inflammatory disorders, such as psoriasis, rheumatoid arthritis, and Crohn's disease.^{60,61} Inhibition of the TNF pathway may increase the patient's susceptibility to both skin and eye infection. The imbalance of TNF- α in the eye is thought to be the etiology of uveitis. Uveitis occurs more commonly in those taking etanercept compared to infliximab and adalimumab.⁶⁰ In addition to uveitis, etanercept has been shown to cause scleritis and orbital myositis. Some patients have also shown a “dechallenge/rechallenge” phenomenon, in which side effects resolve after discontinuation of the drug then return or worsen upon reexposure.⁶² Depending on the etiology, adalimumab and infliximab can also be used to treat uveitis when steroids are ineffective or cause an increase in intraocular pressure. Additional ocular side effects include endogenous endophthalmitis and optic neuritis, which present as blurry vision or a loss of vision.^{61,63,64} These ocular side effects typically develop within 3 to 24 months after the initiation of anti–TNF- α therapy.⁶⁰

Therapy. Patients treated with TNF- α inhibitors should be evaluated at follow-up visits for vision changes and erythema of the eye, because permanent vision loss may result if left untreated. If any ocular symptoms are present, early referral to ophthalmology should be considered. Uveitis, endogenous endophthalmitis, and optic neuritis often resolve with the application of an intraocular topical steroid and discontinuation of the TNF- α inhibitor.^{60,61}

Topical glucocorticosteroids

Key points

- Ocular side effects of periocular and eyelid topical glucocorticosteroid use include decreased wound healing, an increased risk of fungal and bacterial infections, and a

Potential increased risk of glaucoma and posterior subcapsular cataracts

- The risk of ocular side effects from topical glucocorticosteroids is dependent on potency, dosage, and duration of use
- Consider consultation with an ophthalmologist for ocular examination in a patient using periocular or eyelid class III or class IV maintenance topical corticosteroids for >8 weeks

Topical glucocorticosteroids (GCSs) are antiinflammatory drugs that are widely used for the treatment of a variety of mucocutaneous conditions, including atopic dermatitis, contact dermatitis, psoriasis, and allergic conjunctivitis. The most common ocular side effect of periorbital and ocular GCS use is irritation, especially with cream-based preparations compared to ointments. Guin⁶⁵ found that 14% of eyelid dermatitis was caused by allergic contact dermatitis to topical corticosteroids. Additional important side effects include increased intraocular pressure, which can progress to glaucoma, posterior subcapsular cataracts, decreased wound healing, and an increased risk of fungal and bacterial infections.^{66,67}

Topical GCSs inhibit the proliferation, migration, and chemotaxis of fibroblasts, decrease protein synthesis, and decrease cellular mitosis. GCSs also weaken the immune response by inhibiting the secretion of interleukins-1B, -4, -5, and -8, along with other inflammatory proteins. In addition, GCSs heighten the vasoconstrictive effects of epinephrine, while minimizing the inflammatory actions of histamine and bradykinin. These actions lead to the side effects commonly seen in patients using topical GCSs.

In the general population, 5% will experience an increase in intraocular pressure with topical intraocular application of betamethasone microsuspension 0.1% (9-alfa-fluoro-16-methylprednisolone) for 8 weeks.⁶⁸ High-risk patients include those with diabetes, myopia, connective tissue disease, and a positive family history for glaucoma.^{69,70} In patients with established primary open angle glaucoma, 90% will experience ocular hypertension after the intraocular application of betamethasone microsuspension 0.1% for 8 weeks.⁶⁸ The increased intraocular pressure manifests within the first week of topical intraocular corticosteroid use, is asymptomatic or presents as blurred vision, and then resolves within 2 weeks after discontinuation of the topical intraocular corticosteroid.^{69,71} The increased intraocular pressure is a result of corticosteroids stimulating glycosaminoglycan accumulation in the trabecular

Table IV. Drug-related oculocutaneous side effects

syndrome/drug class	Dermatologic side effects	Ocular signs and symptoms	Onset of side effects
SJS and TEN	Epidermal detachment; erythema and erosions; and hypo- or hyperpigmentation	Conjunctivitis; corneal erosion; fornix foreshortening; and symblepharon	24-48 hrs
Retinoids	Alopecia; cheilitis or chapped lips; dermatitis; epistaxis; facial and trunical acne; nail fragility; peeling rash; pruritus; and xerosis	Cataracts; corneal opacities; dryness of the eye leading to discomfort, photophobia, and keratitis; loss of color vision; night blindness; and premacular hemorrhage	1 month
TNF-alpha inhibitors	Acute generalized exanthematosus pustulosis; bacterial infection; cutaneous lymphoma; eczematous dermatitis; erythema multiforme; folliculitis; granuloma annulare; herpes simplex; hyperhidrosis; hyperkeratosis; hyperpigmentation; lichenoid dermatitis; lupus erythematosus; new-onset psoriasis; perniosis-like eruption; rosacea; seborrheic dermatitis; urticaria; and xerosis and pruritus	Endogenous endophthalmitis; optic neuritis; uveitis	Months to years
GCSs	Acne; atrophy; burning and irritation; contact hypersensitivity; decreased elasticity; delayed wound healing; dryness; folliculitis; hypertrichosis; hypopigmentation; miliaria; perioral dermatitis; pruritus; purpura; rosacea; stellate pseudoscars; striae; telangiectasias; ulcerations of the skin; urticaria	Increased ocular pressure; increased risk of fungal and bacterial infections; ocular hypertension; periorbital irritation; posterior cataracts	Minor side effects can start immediately after use, whereas major side effects such as atrophy and rosacea may begin weeks to years after initial GCS use
IFN- α	Hair loss; pruritus; psoriatic skin lesions; sarcoidosis-like lesions	Blurred vision; central retinal vein or artery occlusion; cotton wool spots; exudative hypertensive retinopathy; exudative retinal detachment; ischemic optic neuritis; neovascular glaucoma; panuveitis; retinal hemorrhage; retinal microaneurysm	Within months
EGFR inhibitor	Acneiform eruptions; hyperpigmentation; nail brittleness; paronychia; pruritus and xerosis; scattered telangiectasias; ulcers of oral and nasal mucosa; vaginal dryness	Dry eye; periorbital pruritus and erythema; purulent secretion; trichomegaly leading to conjunctivitis or corneal damage	Dermatologic side effects usually begin days to weeks after initial treatment; nail changes begin 1-2 months after initial treatment; ophthalmologic side effects begin 1-2 months after the initiation of treatment, with trichomegaly being the latest-appearing side effect

Antimalarial drugs (quinine derivatives)	Bluish-black hyperpigmentation of the shins, face, palate, and nails; exfoliative erythroderma; graying of the hair; lichenoid dermatitis; pruritus; urticaria; yellowing of the skin	Cataracts; characteristic retinopathy consisting of hyperpigmentation of the macula surrounded by a zone of depigmentation, which is encircled by hyperpigmentation; corneal deposits; scleral icterus	After 4 months of continuous use
Cyclosporine	Cutaneous BCC and SCC; gingival hyperplasia	Cerebral blindness; hypertrichosis; visual hallucinations	Hypertrichosis occurs shortly after initiation of therapy; gingival hyperplasia occurs after weeks to months; carcinoma occurs after years of cyclosporine use

BCC, Basal cell carcinoma; EGFR, epidermal growth factor receptor; GCs, glucocorticosteroids; IFN, interferon; SCC, squamous cell carcinoma; SJS, Stevens-Johnson syndrome; TEN, toxic epidermal necrolysis; TNF, tumor necrosis factor.

meshwork, thereby increasing the aqueous outflow resistance, leading to decreased outflow.^{71,72} If the pressure stays elevated for a prolonged period of time, cupping of the disc can occur, leading to visual field defects that can be permanent.⁶⁹

In reference to periocular and eyelid topical corticosteroid application, there are a small number of case reports of associated glaucoma with chronic topical corticosteroid application to the eyelids.⁷²⁻⁷⁶ However, in these reports, the patients often had frequent systemic steroid exposure, had an increased risk at baseline, or were incorrectly using a topical class I corticosteroid that resulted in systemic absorption.⁷²⁻⁷⁶ A recent retrospective review in 88 patients with atopic dermatitis using frequent application of class III and IV corticosteroids to the eyelids revealed no increased risk of glaucoma.⁷⁷ In addition, it has recently been shown that only minute amounts of fluticasone propionate 0.005% penetrated eyelid skin, resulting in little to no systemic absorption.⁷⁸ Application of <20 g per week of a class III topical corticosteroid had no significant effect on adrenal function.⁷⁷ Prospective studies are still needed to fully define the risk of glaucoma related to topical periocular corticosteroid use. However, given the theoretical risk of glaucoma and lack of symptoms associated with increased intraocular pressure, it is recommended that patients be questioned relating to blurry vision at their follow-up visits and undergo annual ophthalmologic examinations when using topical corticosteroids periocularly or on the eyelids for >8 weeks. Class I and class II topical corticosteroids are not recommended for periocular or eyelid use.⁷⁶

Posterior subcapsular cataracts are a well-known side effect of systemic corticosteroids at doses of prednisone >15 mg for at least a year.⁶⁹ However, Williamson and Jasani⁷⁹ found that the use of betamethasone disodium phosphate 0.1% intraocularly twice daily for >2 months in 136 eyes resulted in 2 cases of cataracts. However, 1 was present before the steroid therapy and the other was a case of anterior uveitis.⁷⁹ Eight of these 136 eyes were treated for >3 years and none of these developed cataracts.⁷⁹ Posterior subcapsular cataracts are thought to be caused by covalent binding of the corticosteroid to the lens with subsequent oxidation.⁸⁰ Cataract formation has been reported after the administration of corticosteroids via oral, topical use in the periocular region, and subconjunctival routes and nasal sprays. The risk of posterior subcapsular cataracts is also in need of additional prospective studies.

Therapy. Consultation with an ophthalmologist to evaluate intraocular pressure is suggested in

patients consistently using topical class III to IV corticosteroids periocularly or on the eyelids for periods of >8 weeks. In patients with an increased risk of intraocular hypertension at baseline—including those with diabetes, myopia, connective tissue disease, and a positive family history for glaucoma—consideration should be given to the use of alternative agents for the periocular and eyelid areas. If a patient develops any ocular symptoms or vision changes, prompt discontinuation of the GCS and referral to an ophthalmologist is recommended. Intraocular pressures typically elevate within 1 week of topical intraocular GCS use and return to normal within 1 to 2 weeks after discontinuation of topical GCS. However, there are rare case reports of intraocular pressures remaining elevated for months, resulting in glaucoma and requiring surgical correction, but those cases were associated with significant systemic corticosteroid absorption, exposure to systemic steroids, or patients with an increased risk at baseline.^{72,73,75,76}

Interferon-alfa

Key points

- Ocular side effects include a characteristic retinopathy consisting of cotton wool spots, retinal hemorrhages near the optic nerve, microaneurysms, blurred vision, neovascular glaucoma, and increased intraocular pressure
- It has been proposed that treatment with interferon-alfa leads to overstimulation of the immune system, leading to these vascular and inflammatory oculocutaneous side effects
- When intraocular side effects do occur, withdrawal of interferon-alfa therapy and treatment with topical and systemic steroids and immunosuppressive agents if necessary

Interferon-alfa (IFN- α) is a cytokine that activates immune cells, such as macrophages and natural killer cells. IFN- α is commonly used to treat a wide variety of conditions, including hepatitis C, renal cell carcinoma, chronic myelogenous leukemia, multiple myeloma, T cell lymphoma, multiple sclerosis, and melanoma.⁸¹ In patients taking IFN- α , cutaneous side effects include pruritus and psoriatic skin lesions. Ocular side effects include a characteristic retinopathy consisting of cotton wool spots, retinal hemorrhages near the optic nerve, and microaneurysms (Table IV). Blurred vision, neovascular glaucoma, and increased intraocular pressure have also been seen. Rarely, more serious ocular side effects have been reported, including panuveitis, exudative retinal detachment, central retinal vein or

artery occlusion, ischemic optic neuritis, and exudative hypertensive retinopathy.⁸²

It has been proposed that treatment with IFN- α leads to overstimulation of the immune system, leading to these vascular and inflammatory oculocutaneous side effects.⁸¹ These ocular side effects typically begin within a few months of starting IFN- α therapy. Therefore, dermatologists should screen for eye symptoms at follow-up visits and consider referral to an ophthalmologist if appropriate symptoms are detected.^{81,82}

Therapy. When intraocular side effects do occur, the recommended course of treatment is to withdraw IFN- α therapy, treat with topical and systemic steroids, and add immunosuppressive agents if necessary. Unfortunately, some ocular side effects—specifically central retinal vein or artery occlusion, hypertensive retinopathy, and ischemic optic neuritis—may not resolve entirely.⁸²

Epidermal growth factor receptor inhibitor

Key points

- Ophthalmic side effects include trichomegaly, pruritus, erythema of the periorbital skin and eyelids, purulent secretion, and dryness
- It is believed that the amount of epidermal growth factor receptor in basal epidermal cells, sebaceous glands, hair follicle outer root sheath, hair shaft, and capillary system and the function of epidermal growth factor receptor in these sites likely account for the majority of the oculocutaneous side effects
- Preservative-free moisturizing eye drops and bedtime ointments or those containing antibiotics and/or steroids can be used for the treatment of ocular side effects and lead to their resolution

Epidermal growth factor (EGF) is a protein that assists in cell proliferation and differentiation during normal growth and wound healing. EGF receptor (EGFR) inhibitors are approved for the treatment of solid tumor cancers caused by upregulation of EGF. These include non–small cell lung cancer, pancreatic cancer, breast cancer, and colon cancer.

The most commonly reported ocular change with EGFR inhibitor use is excessive growth of the eyelashes (trichomegaly) and inward growth of the eyelashes (trichiasis), which can affect the patient's vision and lead to ingrown hairs, conjunctivitis, and corneal damage.^{83,84} Corneal abrasions quickly progress to corneal ulcerations caused by abnormal epithelial and wound healing induced by the EGFR inhibitor. Therefore, the prompt treatment of any

abrasion is necessary to prevent ulceration. Other ophthalmic side effects include pruritus, erythema of the periorbital skin and eyelids, purulent secretion, and dryness. These side effects have been noted within 1 to 2 months of initial EGFR inhibitor use.⁸³ Trichomegaly is the latest-appearing side effect, starting at around 10 weeks.⁸⁴ Dermatologic side effects of EGFR inhibitors can be seen in Table IV.

While the exact pathogenesis of EGFR inhibitor side effects is unknown, it is believed that the amount of EGFR in basal epidermal cells, sebaceous glands, hair follicle outer root sheath, hair shaft, and capillary system and the function of EGFR in these sites likely account for the majority of the oculocutaneous side effects, including trichomegaly and trichiasis.^{85,86} Hypersensitivity reactions, both immediate and delayed, lead to the eyelid dermatitis and blepharitis seen in some patients taking EGFR inhibitors.⁸³

Therapy. Preservative-free moisturizing eye drops and bedtime ointments or those containing antibiotics and/or steroids can be used for the treatment of ocular side effects and lead to their resolution.⁸³ There are currently no therapies available for trichomegaly apart from discontinuation of the EGFR inhibitor.⁸⁵ If trichiasis causes corneal abrasions, then antibiotic eye drops are recommended to prevent infection, along with appropriate trimming of the eyelashes and epilation of any “turned in” eyelashes using the slit lamp microscope. In addition, bandage contact lenses are placed to protect the corneal surface, with punctal plugs used as needed in this situation. If patients experience visual disturbances or ocular discomfort, referral to the ophthalmology department should be strongly considered to rule out corneal ulceration.

Antimalarial drugs

Key points

- **Fifty percent of patients treated with quinine derivatives present with ocular side effects**
- **Ocular manifestations include yellowing of the sclera, cataracts, corneal deposits, and a unique retinopathy**
- **If retinopathy is suspected, the offending drug must be discontinued immediately**

Antimalarial drugs, namely chloroquine and quinine derivatives, are used to treat lupus erythematosus and other autoimmune conditions in addition to malaria. In patients treated with quinine derivatives, 30% present with cutaneous side effects (Table IV) and 50% present with ocular side effects.⁸⁷⁻⁹⁰ Quinine is the most common antimalarial drug known to cause ocular side effects, with chloroquine second and hydroxychloroquine third.^{89,90} The

combination of chloroquine and hydroxychloroquine compounds the ocular side effects. Therefore, if combination therapy is required, quinacrine should be added to chloroquine or hydroxychloroquine (preferentially the latter), because quinacrine does not lead to ocular side effects.⁸⁷ As early as 2 weeks after initiation of treatment, patients may experience yellowing of the sclera, cataracts, and corneal deposits (corneal verticillata) that lead to vision changes.^{87,89,90} The most severe side effect, though rare, is a retinopathy that presents as hyperpigmentation of the macula surrounded by a zone of depigmentation, which is encircled by hyperpigmentation, resembling a bull's eye. This retinopathy can lead to permanent vision loss and therefore requires timely ophthalmologic evaluation.⁹¹

While the exact mechanism leading to these oculocutaneous side effects is unknown, exposure to light is a likely contributing factor. Antimalarial agents absorb sunlight, and as a result form free radicals and reactive oxygen species, which lead to tissue damage.⁸⁹ These antimalarial medications are deposited in melanin-containing tissues; therefore, the eyes and skin experience increased drug concentrations, leading to the aforementioned oculocutaneous side effects.⁹¹

Most of these side effects can be avoided by ensuring that the patient is taking an appropriate dose, wearing sunglasses and protective clothing, and importantly, confirming that the patient has an ophthalmologist. Side effects can be reversed by discontinuing treatment with the causative antimalarial drug.⁹¹ An ophthalmologic consultation should be considered within 4 months of initiation of hydroxychloroquine, quinine, or chloroquine.⁹² Subsequent to the baseline examination, annual examinations no later than 5 years after starting antimalarial therapy are encouraged.⁹² Screening is aimed at early detection, with the goal being to recognize early signs of paracentral field loss or paracentral tissue damage before the development of the bull's eye retinopathy.

Antimalarial drugs, most commonly hydroxychloroquine, when taken for >5 years, may lead to optic neuropathy. This risk is highest when doses of hydroxychloroquine exceed 400 mg daily or 6.5 mg/kg/day (ideal body weight) and when doses of chloroquine exceed 250 mg daily or 3.0 mg/kg/day based on ideal body weight in individuals with short stature.⁹² The most current literature suggests the cumulative dose as opposed to the daily dose as the most important aspect in determining risk for toxicity, with the thresholds for hydroxychloroquine being 1000 g and 460 g chloroquine.⁹² Duration of therapy is also evaluated by the ophthalmologist, with treatment

for <5 years showing fewer ocular side effects.⁹² Finally, liver and renal health of the patient is evaluated because a decrease in their function can add to the risk to the eyes; antimalarial drugs are metabolized by both the liver and the kidney.⁹² If the daily dose is greater than the amounts listed above, the duration of use is >5 years, or there are liver or renal issues, patients should seek ophthalmologic follow-up every 6 months because they are at an increased risk of toxicity.⁹² In addition, if patients develop any new visual symptoms, including reduced visual sensitivity, reading difficulty, or blind spots, prompt ophthalmologic examination is recommended.

Therapy. If retinopathy is suspected, the offending drug must be discontinued immediately. While discontinuation usually leads to partial recovery of visual acuity, there are reports of continued long-term loss of vision after discontinuation of the offending antimalarial agent.^{87,91,93} Patients with preservation of the external limiting membrane of the retina show increased rate of visual improvement upon cessation of the drug.⁹⁶

Cyclosporine

Key points

- Cyclosporine is a calcineurin inhibitor that minimizes the activation and maturation of interleukins and T cells involved in cell-mediated immunity
- Ocular side effects include trichomegaly, visual hallucinations, cerebral blindness, bushy eyebrows, and increased hair growth
- If ocular symptoms are noted, ophthalmologic referral should be considered so that appropriate treatment can be introduced and potential blindness avoided

Cyclosporine is a calcineurin inhibitor that reversibly inhibits the transcription of interleukin-2 and several other cytokines, mainly in T helper cells, thereby inhibiting the activation and maturation of cells involved in cell-mediated immunity. Because of its immunosuppressive properties, cyclosporine is used not only for prophylaxis and treatment of transplant rejection, but also a multitude of other immunoregulatory disorders, including psoriasis, atopic dermatitis, Behcet disease, rheumatoid arthritis, Crohn's disease, and aplastic anemia.⁹⁴

The most serious side effects of cyclosporine use are nephrotoxicity and hypertension. However, oculocutaneous side effects have also been reported.^{95,96} These include trichomegaly, visual hallucinations, and cerebral blindness.⁹⁷ Bushy eyebrows and even increased growth of eyelashes are commonly seen within 2 to 3 months of initiation of cyclosporine, even in the lower doses (3-5 mg/kg/

day) used for psoriasis and atopic dermatitis. Other side effects may take months or years to develop. Symptoms typically will reverse upon the discontinuation of cyclosporine, which seldom is used for >6 to 9 months in the aforementioned 2 dermatoses.^{95,98} The concurrent use of systemic glucocorticoids and cyclosporine has also been shown to exacerbate the cataract formation caused by systemic glucocorticoids.⁹⁶

Therapy. For patients receiving treatment with cyclosporine, questioning them regarding vision changes is recommended at follow-up visits to allow for the early detection and prevention of severe adverse events. If ocular symptoms are noted, then referral to an ophthalmologist should be considered to allow for appropriate therapy and the avoidance of potential blindness.

CONCLUSION

In this 2-part review of infectious, inflammatory, genetic, and neoplastic diseases as well as drug-related effects mutual to the skin and eye, the importance of the dermatologist's role in diagnosis, continuing care, and close collaboration with ophthalmologists has been fully reviewed. When evaluating a patient with each of the diseases mentioned in this review, it is essential for dermatologists to question patients on visual changes, including blurring or vision loss of any kind. A thorough examination of the eye and the periocular skin is also important in all patients, because many periocular lesions and tumors spread locally to involve the eye itself. In addition, as mentioned in a number of the described conditions, the appearance of the periocular skin, eyelid, and conjunctiva may be a marker for the health of the eye. If eye pathology is suspected, dermatologists should consult with their ophthalmology colleagues with an urgent request in diseases such as herpes zoster, SJS, and TEN. By doing so, the dermatologic community can play an important role in helping prevent the multitude of ocular complications associated with the host of diseases discussed in this 2-part series, including diminished or loss of vision and even complete blindness.

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Topical pharmacotherapy for skin cancer

Part I. Pharmacology

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After completing this learning activity, participants should be able to describe the mechanisms of action of established and newly emerging topical treatments for skin cancer and identify indications and contraindications for the use of topical therapies in the treatment of skin cancer.

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Topical pharmacotherapy represents an effective alternative treatment for superficial skin cancer, primarily actinic keratoses and basal cell carcinomas. We provide an in-depth analysis of the pharmacologic aspects of available topical drugs for the treatment of primary skin tumors. In particular, we evaluate the mechanisms of action, formulations and indications, side effects, and contraindications of 5-fluorouracil, imiquimod, diclofenac, ingenol mebutate, and retinoids. Moreover, the characteristics of some investigational molecules (ie, resiquimod, piroxicam, dobesilate, and betulinic acid) are presented. (J Am Acad Dermatol 2014;70:965.e1-12.)

Key words: 5-fluorouracil; betulinic acid; diclofenac; dobesilate; imiquimod; ingenol mebutate; piroxicam; resiquimod; retinoids; skin cancer.

INTRODUCTION

Since the introduction of 5-fluorouracil in the 1960s,¹ a number of topical drugs have been used for the treatment of skin tumors. Some of these topical drugs have been approved by the US Food and Drug Administration for selected indications; others are used off-label or are under investigation.

The purpose of this review is to provide an in-depth analysis of the available topical treatments for primary skin cancers (Table I), including their mechanism of action, formulations, indications, side effects, and contraindications. The effectiveness of these drugs in the treatment of skin cancer, according to evidence-based medicine guidelines, is evaluated in part II of this continuing medical education article.

5-FLUORURACIL

Key points

- **5-Fluorouracil acts as an antimetabolite, interfering with DNA synthesis**
- **Topical 0.5%, 1%, 2%, and 5% 5-fluorouracil are approved by the US Food and Drug Administration for the treatment of actinic keratoses**
- **The 5% formulation is also approved by the US Food and Drug Administration for the treatment of superficial basal cell carcinomas**
- **The most common local skin reactions observed during treatment with 5-fluorouracil include erythema, blistering, necrosis, and erosions, accompanied by pruritus and burning**

5-Fluorouracil (5-FU) is a structural thymidine analogue that was pioneered by the Lasker Award-winning father of topical cancer immunotherapy Edmund Klein in the 1960s.¹⁻³

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Abbreviations used:

5-FU:	5-fluorouracil
AK:	actinic keratosis
BCC:	basal cell carcinoma
BD:	Bowen disease
DHA:	diclofenac 3% gel in 2.5% hyaluronic acid
EPD:	extramammary Paget disease
EQ:	erythroplasia of Queyrat
IM:	ingenol mebutate
IQ:	imiquimod
LM:	lentigo maligna
LSR:	local skin reaction
NSAID:	nonsteroidal antiinflammatory drug
RQ:	resiquimod

Mechanism of action

5-FU acts as an antimetabolite, binding to thymidylate synthase through the cofactor 5,10-methylene tetrahydrofolate. As a result, the enzyme is inhibited and conversion of deoxyuridine to thymidine nucleotides fails, leading to reduced DNA synthesis, a decrease in cell proliferation, and the induction of cell death (Fig 1). These effects are particularly evident in cells with high mitotic rates, such as neoplastic cells.⁴⁻⁷ No concurrent immunomodulatory mechanism has been identified to our knowledge, but the intense inflammation caused by 5-FU might contribute to its antitumoral effects.⁸

Formulations and indications

Topical formulations of 0.5% (cream), 1% (cream), 2% (solution), and 5% (cream and solution) 5-FU are available for the treatment of skin cancer. The classic 5% 5-FU formulation consists of a cream also containing white petrolatum, stearyl alcohol, propylene glycol, polysorbate 60, and paraben. The 0.5% 5-FU cream has an innovative formulation, being delivered via a patented porous microsphere

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Table I. Topical drugs used for the treatment of skin cancer

Drug	Available strengths	Official oncologic indications	Off-label/investigational oncologic indications	Pregnancy category	Mechanism of action
5-fluorouracil	0.5%, 1%, 2%, and 5%	AKs and superficial BCCs (approved by the FDA)	BD, SC, EQ, EPD, and melanoma metastases	X	Interference with DNA synthesis
Imiquimod	2.5%, 3.75%, and 5%	AKs and superficial BCCs (approved by the FDA)	Nodular BCCs, BD, LM, EQ, EPD, melanoma metastases	C	Modification of immune response
Diclofenac	3% gel in 2.5% hyaluronic acid	AKs (approved by the FDA)	BD	B	Increased apoptosis through cyclooxygenase inhibition
Ingenol mebutate	0.015% and 0.05% gel	AKs (approved by the FDA)	BCCs	C	Induction of direct cellular death and inflammatory response
Retinoids	Tretinoiin 0.05% and 0.1% cream; isotretinoiin 0.1% cream; adapalene 0.1% and 0.3% gel; and tazarotene 0.1% gel	—	AKs, LM, and BCCs	C (tretinoiin, adapalene) X (tazarotene)	Control of cell proliferation and differentiation
Resiquimod*	0.01%, 0.03%, 0.06%, and 0.1% gel	—	AKs	—	Modification of immune response
Piroxicam	1% gel	—	AKs	C	Increased apoptosis through cyclooxygenase inhibition
Dobesilate*	Calcium dobesilate 2.5% and potassium dobesilate 5%	—	AKs and BCCs	—	Inhibition of fibroblast growth factors
Betulinic acid*	Galenic preparations (ointment and oleogel)	—	AKs	—	Cytotoxic, antiproliferative, and apoptotic effects

AK, Actinic keratosis; BCC, basal cell carcinoma; BD, Bowen disease; EPD, extramammary Paget disease; EQ, erythroplasia of Queyrat; FDA, US Food and Drug Administration; LM, lentigo maligna; SC, solar cheilosis.

*Not commercially available.

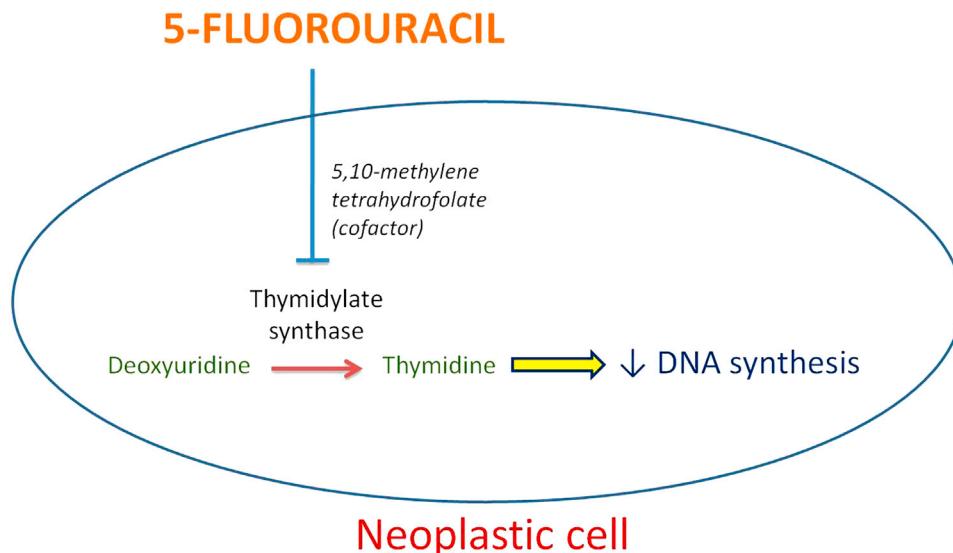


Fig 1. Primary mechanism of action of 5-fluorouracil: inhibition of thymidylate synthase, resulting in reduced DNA synthesis, a decrease in cell proliferation, and the induction of cell death.

system comprised of methyl methacrylate/glycol dimethacrylate cross polymer and dimethicone, which improves drug penetration and availability.⁹ Recently, a new formulation containing 0.5% 5-FU in combination with 10% salicylic acid solution¹⁰ has been marketed in some European countries, including the United Kingdom and Switzerland. In some countries, such as Italy, 5-FU is not currently available in any formulation.

Topical 1%, 2%, and 5% 5-FU are approved by the US Food and Drug Administration (FDA) for the treatment of actinic keratoses (AKs) of any localization (2 applications daily for 2–4 weeks); the 0.5% cream is approved only for face and scalp AKs (1 application daily for 2–4 weeks). The 5% formulation is also approved by the FDA for the treatment of superficial basal cell carcinomas (BCCs) when conventional methods are impractical (for example, in cases of multiple lesions or difficult treatment sites) using 2 applications daily for 2–4 weeks. The use of 5% 5-FU in the treatment of Bowen disease (BD) is off-label.^{11,12}

Side effects and contraindications

The most common local skin reactions (LSRs) observed during treatment with 5-FU include erythema, blistering, necrosis, and erosions, accompanied by pruritus and burning.^{1,4,7,10} Exposure to sunlight may also increase the intensity of these reactions. Residual hypo- or hyperpigmentation may occur. Eye irritation, conjunctivitis, keratitis, and some cases of ectropion

have been reported during treatment of periocular lesions, but completely resolved after discontinuation of therapy.^{8,13,14} Although little 5-FU is absorbed from normal skin, about 20% can reach the bloodstream when it is applied to damaged skin. One case report described a patient with severe dehydropyrimidine dehydrogenase (DPD) deficiency (the primary enzyme involved in degradation of the drug), treated with standard doses of topical 5-FU for a BCC, who developed severe gastrointestinal and hematologic toxicity in conjunction with a flare of inflammatory bowel disease.¹⁵ Although it is difficult to conclude that DPD deficiency is an absolute contraindication for topical 5-FU, given the extremely low absorption rates, a warning appears in the package insert of the drug. 5-FU should not be used in women who are or may become pregnant because it is teratogenic and appears in FDA pregnancy category X.

Comments

5-FU has been used for decades in the treatment of some forms of skin cancer. It has a good safety profile and requires a relatively short treatment course (2–4 weeks). Among multiple available concentrations, the 5% concentration is most versatile, being able to be used in AKs, superficial BCCs, and BD. In general, the efficacy of 5-FU is dose-related and depends upon skin barrier penetration of the applied formulation; thicker, hypertrophic lesions may need to be pretreated with keratolytic agents or gentle curettage.⁴ The

LSRs caused by 5-FU are predictable and required in order to achieve a positive therapeutic outcome, although they may limit tolerability in some patients. They are related to concentration and dosing,^{4,16} although it has been our experience (and that of most authors) that patients with an intense inflammatory response often attain the best clinical response.⁴ In any case, LSRs progressively improve as application frequency is reduced or treatment is discontinued. If severe, they should be managed with topical steroids. In addition, certain areas are more sensitive to severe irritation, including skin folds, the lips, and eyelids. Special care should be given to the treatment of periocular lesions, avoiding direct contact of 5-FU to the eye, especially the conjunctiva.

IMIQUIMOD

Key points

- Imiquimod is a synthetic immune response modifier
- Imiquimod 5%, 3.75%, and 2.5% cream are approved by the US Food and Drug Administration for face and scalp actinic keratoses
- Imiquimod 5% is also approved by the US Food and Drug Administration for the treatment of superficial basal cell carcinomas
- Patients treated with imiquimod may experience moderate to severe local skin reactions, occasionally extending beyond the application site, including pruritus, burning, erythema, vesicles, erosions, exudation, and crusting
- The development of such inflammatory reaction is a good predictor of therapeutic efficacy

Imiquimod (IQ) is a synthetic imidazoquinoline amine that was the first of a new class of topical immune response modifiers. It was originally approved by the FDA in 1997 for the treatment of external genital and perianal warts.

Mechanism of action

The mechanism of action of IQ mainly acts upon Toll-like receptors (TLRs) that are located on the surface of antigen-presenting cells (ie, dendritic cells, monocytes/macrophages, and Langerhans cells¹⁷⁻¹⁹). IQ acts as a potent TLR-7 and -8 agonist, leading to activation of a central transcription factor, nuclear factor-kappa B (NF- κ B). Stimulation of TLR-mediated signaling pathways results in the production and release of several endogenous cytokines and chemokines, such as tumor necrosis factor- α (TNF- α), interferon gamma (IFN- γ),

IFN- α , interleukins (ILs)-6, -1a, -1b, -8, and -12, granulocyte macrophage colony-stimulating factor, and granulocyte colony-stimulating factor.⁸ They, in turn, stimulate both innate and acquired immune response pathways (Fig 2), resulting in IQ antitumor activity.^{8,17-19} Moreover, several studies have shown that IQ has antiangiogenic properties and provided evidence for its role in the inhibition of pathologic growth of new vessels.^{8,20} In particular, IQ increases levels of IL-10 and IL-12, both of which inhibit angiogenesis and decrease cellular production of several proangiogenic factors (eg, fibroblast growth factor, IL-8, and urokinase plasminogen activator), inhibit vascular motility and invasion, and induce endothelial cell apoptosis. It is likely that these factors mediate the production of IFN- γ , the most important inhibitor of angiogenesis.⁸ Also, IQ may facilitate production of proapoptotic signaling, including the Fas receptor (FasR) belonging to the necrosis factor receptor family.²¹ By binding a FasR ligand, namely the Fas ligand L (FasL), it stimulates a cascade of events, including caspase activation, ultimately leading to cellular death of tumor cells.²¹ More recently, it has been suggested that IQ may play a role in the lymphatic transport of immune cells and factors with subsequent immunologic destruction of tumors, not only in the treated area, but also in those areas located between the IQ application site and the regional lymph nodes (the “lymphatic field clearance”²²).

Formulations and indications

Topical formulations of 5%, 3.75%, and 2.5% IQ cream are currently available. The 5% cream is now off-patent and is being manufactured in a generic form by a number of companies. All formulations are approved by the FDA for face and scalp AKs in immunocompetent individuals; the 5% cream may be used for the treatment of a surface area of up to 25 cm², and the other formulations may be used for the treatment of larger areas, up to 200 cm². In the treatment of AKs, the standard schedule adopted in the United States consists of 2 applications per week for 16 weeks, while the preferred schedule in the European countries consists of 1 to 2 courses of treatment 3 times per week for 4 weeks.⁹ The treatment regimens of IQ 3.75% and 2.5% cream for AKs consist of once-daily application for two 2-week treatment cycles, separated by a 2-week no-treatment interval. All formulations should be applied on the lesions before going to bed, left on for 8 hours, and washed off in the morning with water and mild soap.

IQ 5% is also approved by the FDA for the treatment of superficial BCCs, with a schedule of

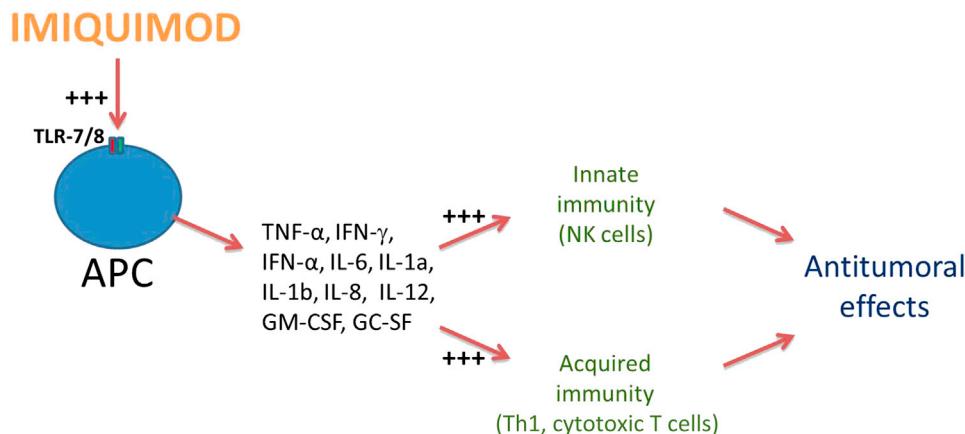


Fig 2. Primary mechanisms of action of imiquimod. *APC*, Antigen-presenting cell; *GC-SF*, granulocyte colony-stimulating factor; *GM-CSF*, granulocyte-macrophage colony-stimulating factor; *IFN*, interferon; *IL*, interleukin; *TLR*, Toll-like receptor; *TNF*, tumor necrosis factor.

5 applications per week for 6 weeks.^{17,23} Moreover, it has been used off-label in other types of skin cancer, such as nodular BCCs, BD, erythroplasia of Queyrat (EQ), extramammary Paget disease (EPD), lentigo maligna (LM), and melanoma metastases.^{17,24-29}

Side effects and contraindications

Patients treated with IQ may experience moderate to severe LSRs, occasionally extending beyond the application site, including pruritus, burning, erythema, vesicles, erosions, exudation, and crusting.^{7,30} Generally, the cosmetic outcome is good,⁶ but persistent pigmentary changes may sometimes occur. Although no potential for inducing either photocontact allergy or phototoxicity has been shown,³¹ avoiding or minimizing exposure to sunlight (including sunlamps) because of concern for heightened sunburn susceptibility is mentioned in the package insert of the drug. Regarding the use of IQ in the treatment of periocular lesions, conjunctivitis and keratitis may occur only after direct contact of the cream with the mucosal surface.³² Rarely, the onset of other cutaneous disorders, such as psoriasis, pemphigus foliaceus, aphthosis, vitiligo, angioedema, and eruptive epidermoid cysts may be observed.¹⁷ Regarding the systemic side effects of IQ, flu-like or gastrointestinal symptoms, such as fatigue, fever and chills, arthralgias, myalgias, nausea, and diarrhea may rarely occur, especially when larger areas are treated.^{7,9,17} The use of IQ during pregnancy should be discouraged (FDA pregnancy category C).

Comments

In recent years, IQ 5% cream has given a great boost to the topical treatment of skin cancer.

Similarly to 5-FU, the development of a brisk inflammatory reaction is a good predictor of therapeutic efficacy. The recent introduction of the more tolerable 2.5% and 3.75% strength formulations for AKs allows for the treatment of large skin areas, the full face, and the balding scalp.³³ LSRs of IQ can be generally managed without additional complications using cold compresses, wet dressing, skin care ointments, and/or topical antiseptics; in severe reactions, a temporary discontinuation for 1 to 3 weeks is required.³⁴ Topical steroids should not be used to manage side effects, because they may impair the immunologic reactions needed for therapeutic efficacy.³⁴ The patient should be properly instructed about the potential side effects of this medication.

DICLOFENAC

Key points

- **Diclofenac acts by downregulating cyclooxygenase enzymes and increasing apoptosis**
- **A unique topical formulation containing diclofenac 3% gel in 2.5% hyaluronic acid is approved by the US Food and Drug Administration for the treatment of actinic keratoses**
- **Diclofenac 3% gel in 2.5% hyaluronic acid is considered a well-tolerated treatment, with mild irritant side effects at application sites**

Diclofenac is a potent nonsteroidal antiinflammatory drug (NSAID).

Mechanism of action

Diclofenac acts by downregulating cyclooxygenase enzymes, primarily cyclooxygenase-2 (COX-2). Based on the evidence that arachidonic acid metabolism upregulation may promote carcinogenic

effects by stimulating angiogenesis, inhibiting apoptosis, and increasing the invasiveness of tumor cells.^{35,36} NSAIDs may be effective in reducing dysplastic keratinocytes in cancerous lesions, including AKs, by stimulating programmed cell death via COX-2 inhibition.³⁷ Moreover, topical diclofenac upregulates apoptosis by sensitizing neoplastic keratinocytes for ligand-induced death.³³ Additional mechanisms of action explain its therapeutic benefit by alteration of cell proliferation and the inhibition of angiogenesis.^{37,38}

Formulations and indications

A unique topical formulation containing diclofenac 3% gel in 2.5% hyaluronic acid (DHA) is currently available. The hyaluronic acid vehicle acts by delivering and then retaining diclofenac in the epidermis.³⁹ DHA is approved by the FDA for the treatment of AKs with a regimen consisting of twice daily applications for up to 12 weeks. It has been also used off-label in the treatment of BD.⁴⁰

Side effects and contraindications

Mild irritant side effects at application sites are reported during the application of DHA, such as pruritus, erythema, dry skin, and exfoliation, all with a satisfactory cosmetic outcome.³⁶ Although rare, photosensitivity and photocontact dermatitis may occur, and patients should be advised to avoid sun exposure.^{4,36} The use of DHA should be avoided in patients with NSAID hypersensitivity.⁴ Because some cases of upper gastrointestinal bleeding were reported with a topical antiinflammatory gel formulation of diclofenac, the use of DHA is discouraged in patients with known bleeding diatheses, although its systemic absorption appears to be minimal.³⁶ This drug is FDA pregnancy category B.

Comments

The overall efficacy of DHA in treating AKs is lower than that reported with other topical treatments (as discussed in part II of this continuing medical education article). It is considered a well-tolerated treatment for AKs, with patient compliance being good despite the double daily application for 3 months. Based on this, it represents an alternative therapy for patients who are not willing to endure the side effects associated with 5-FU or IQ.⁴ In rare cases of more intense reactions, the possible onset of allergic contact dermatitis should be considered and confirmed by patch testing.³⁶ Another advantage of DHA is represented by its pregnancy category B classification, which allows for safer use compared to other topical

medications in women of childbearing age with AKs (with today's lifestyles these patients are increasingly common).⁴

INGENOL MEBUTATE

Key points

- **Ingenol mebutate has a dual mechanism of action: the induction of rapid cellular death (within a few hours) followed by an inflammatory response (within days)**
- **Two formulations of ingenol mebutate are available and approved by the US Food and Drug Administration for the treatment of actinic keratoses: a 0.015% gel for the face and scalp lesions once daily for 3 days and a 0.05% gel for the trunk and extremities once daily for 2 days**
- **The most common local skin reactions related to the use of ingenol mebutate include erythema, flaking/scaling, and crusting**

Ingenol mebutate (IM), a macrocyclic diterpene ester, is a recently marketed natural extract from *Euphorbia peplus*. The sap of this plant has long been used as a topical traditional remedy for common skin lesions, such as warts and neoplasms.^{41,42}

Mechanism of action

IM has a dual mechanism of action: the induction of rapid cellular death in the treated area, beginning a few hours after application, followed by an inflammatory response within days of application, able to eliminate residual cells⁴³ (Fig 3). Death of dysplastic keratinocytes appears to be caused by direct cell necrosis rather than apoptosis, and is related to mitochondrial swelling and chemoablation and disruption of the plasma membrane. The inflammatory response is both caused by cellular necrosis and directly induced by IM through protein kinase C activation, able to stimulate proinflammatory cytokines release, endothelial adhesion molecule expression, and the production of tumor-specific antibodies, leading to a neutrophil-mediated antibody-dependent cellular cytotoxicity.⁴³⁻⁴⁵

Formulations and indications

Two formulations of IM are available and approved by the FDA for AKs: a 0.015% gel for face and scalp lesions used once daily for 3 days and a 0.05% gel for the trunk and extremities used once daily for 2 days. The gel may be applied to the affected area and up to 1 contiguous skin area of approximately 25 cm². Experimental studies suggest a possible use for the treatment of BCCs.⁴⁶

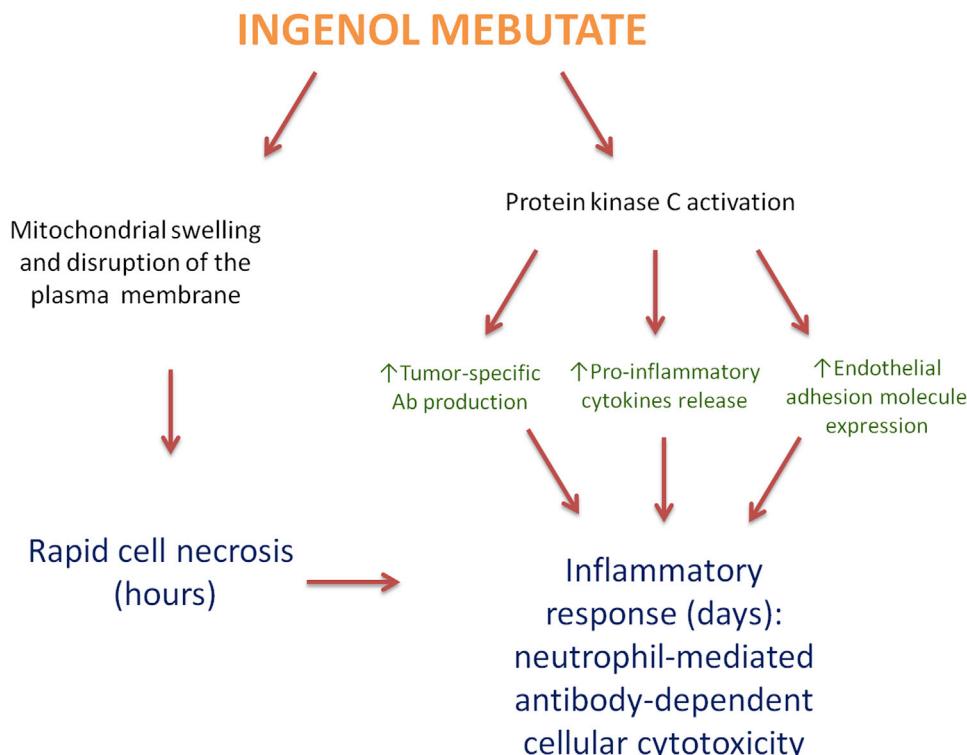


Fig 3. Dual mechanism of action of ingenol mebutate.

Side effects and contraindications

The most common LSRs related to the use of IM include erythema, flaking/scaling, and crusting. Moreover, swelling, blistering, pustulation, and erosions/ulceration may occur. They are more intense between days 3 and 8 from the beginning of treatment. However, symptoms are transient and resolve spontaneously, generally within 2 (face and scalp) to 4 (trunk and extremities) weeks after discontinuation. No scarring has been reported.^{41,43} Patient adherence in a clinical setting was excellent.⁴⁷ There are no adequate and well-controlled studies for the use of IM gel in pregnant women (FDA pregnancy category C).

Comments

IM is the most recent medication for AKs that has been approved by the FDA. This treatment option is appealing for its short treatment schedule (2-3 applications), which may facilitate adherence to therapy, especially for noncompliant patients who are unenthusiastic about longer treatment courses.⁴⁸ Patients should wash their hands immediately after applying IM gel and be careful not to transfer the applied drug to other areas, especially the eye and the periocular area. If accidental exposure occurs, the area should be flushed with water and treated with topical steroids.

RETINOIDS

Key points

- Retinoids interfere with cell proliferation and differentiation through their interaction with specific cellular and nuclear receptors
- Topical retinoids used off-label in the treatment of skin cancer include tretinoin, isotretinoin, adapalene, and tazarotene
- Topical retinoids may be responsible for mild to moderate local side effects, including erythema, peeling, dryness, burning, and pruritus

Retinoids include a variety of vitamin A (retinol) derivatives that are commercially available for the treatment of acne, psoriasis, and skin aging. Topical retinoids used in the treatment of skin cancer include tretinoin, the acid form of vitamin A, also known as all-trans retinoic acid, which is the active vitamin A metabolite in several tissues, isotretinoin (13-cis-retinoic acid), and two third-generation retinoids, adapalene and tazarotene.

Mechanism of action

Vitamin A is necessary for the growth and differentiation of epithelial tissues. Retinoids are known to influence these processes through their interaction with specific cellular and nuclear receptors. The cellular or cytoplasm receptors include

the cellular retinoic acid binding protein (CRABP) types I and II and the cellular retinol binding protein.⁴⁹ The nuclear retinoic acid receptor (RARs) are related to a super family of nuclear DNA transcription factors, which include steroid, thyroid hormone, and vitamin D receptors, and comprise 3 forms: RAR- α , RAR- β , and RAR- γ .⁴⁹ Tretinoin and isotretinoin represent nonspecific RARs agonists, while adapalene and tazarotene selectively bind to the RAR subtypes β and γ . As a consequence, retinoids control cell proliferation and differentiation and might potentially interfere with the tumor promotion phase of carcinogenesis by inducing apoptosis.^{7,50,51}

Formulations and indications

Available topical formulations used in the treatment of cancerous lesions include tretinoin 0.05% and 0.1% cream, isotretinoin 0.1% cream (not commercially available in the United States), adapalene 0.1% and 0.3% gel, and tazarotene 0.1% gel. None of these formulations have been approved by the FDA for the treatment of skin cancer, but they have been used off-label, either alone or in association with other modalities, in the treatment of AKs and, experimentally, of BCCs and LM.⁵²⁻⁵⁵

Side effects and contraindications

Topical retinoids may be responsible for mild to moderate local side effects, including erythema, peeling, dryness, burning, and pruritus. Tretinoin may cause skin irritation; patients exposed to ultraviolet light irradiation may exacerbate their discomfort. It appears to be neither phototoxic nor photoallergic *in vivo*.⁵⁶ Tretinoin and adapalene are classified as pregnancy category C, and tazarotene is classified as pregnancy category X. There are no FDA recommendations for topical isotretinoin; however, as for systemic isotretinoin (pregnancy category X), its use during pregnancy is not recommended.

Comments

In the past, topical retinoids, especially tretinoin, were frequently used off-label to treat AKs; in recent years, the introduction of other treatments approved by the FDA has significantly reduced their use, because they are not devoid of local side effects that may lead to discontinuation or non-compliance.

EMERGING THERAPIES

Key points

- **Resiquimod is an immune response modifier investigated for the topical treatment of actinic keratoses**

- **Piroxicam, a NSAID that inhibits the activity of COX-1 and COX-2, is being evaluated as a possible agent in the treatment of actinic keratoses**
- **Topical experimental formulations containing calcium dobesilate 2.5% and potassium dobesilate 5% have been utilized for the treatment of basal cell carcinomas and actinic keratoses**
- **Betulinic acid is a natural compound that exerts cytotoxic, antiproliferative, and apoptotic effects on tumor cells. Galenic preparations containing betulinic acid have been experimentally utilized in the treatment of actinic keratoses**

Resiquimod (RQ) is an investigational immune response modifier, TLR-7 and TLR-8 agonist, that activates both myeloid and plasmacytoid dendritic cells. In addition, it promotes endogenous cytokine release, such as interleukin-6 (IL-6), TNF- α and IFN- γ , more effectively than IQ.^{41,57,58} It also induces the IL-1 receptor antagonist (IL-1ra), granulocyte colony stimulating factor (G-CSF), granulocyte macrophage-colony stimulating factor (GM-CSF), macrophage inflammatory protein (MIP)-1 α , MIP-1 β , and monocyte chemotactic protein (MCP-1).^{44,57} Topical gel formulations containing different concentrations (0.01%, 0.03%, 0.06% or 0.1%) of RQ have been investigated in the topical treatment of AKs.^{44,57} In general, both local and systemic side effects of RQ gel are similar to those observed with IQ. In a study, the 0.01% regimen was well tolerated and the RQ 0.03% regimen adequately tolerated, while 0.06% and 0.1% regimens were considered not adequately tolerated.⁵⁷

Piroxicam is a nonselective NSAID that inhibits the activity of COX-1 and COX-2 that are both involved in skin tumorigenesis. As a consequence, it induces apoptosis, and inhibits angiogenesis, recruitment of growth factors, immunosuppression, and production of carcinogenetic mediators, limiting tumor invasiveness.⁵⁹ A topical gel formulation containing 1% piroxicam has been evaluated as a possible agent in the treatment of AKs.^{59,60} Mild to moderate local side effects, including pruritus, erythema, dry skin and, rarely, rash, have been reported with the use of the gel.⁶⁰ As for other NSAIDs, the known effects on the fetal cardiovascular system limit the use of topical piroxicam during pregnancy (FDA pregnancy category C).

Dobesilate is a synthetic investigational topical agent that exerts anti-tumorigenic effects through inhibition of fibroblast growth factors (FGFs). These

ubiquitously expressed transmembrane signaling molecules are involved in many biological processes including proliferation, differentiation, angiogenesis, cell migration and survival. FGFs are upregulated in skin cancers, playing a pivotal role in cancer development, invasion and metastasis.⁶¹⁻⁶³ The blocking of FGFs results in inhibition of cell viability, angiogenesis and tumor spread, as demonstrated in animal studies.⁶² Topical experimental formulations containing dobesilate 2.5% and 5% have been utilized for the treatment of BCCs and AKs.⁶¹⁻⁶³ In these preliminary studies, mild pruritus and stinging were local effects observed in some patients.⁶²

Betulinic acid is an investigational, antineoplastic natural compound, mainly contained in birch tree bark. Pentacyclic triterpenes are a class of compounds extensively studied as anticancer agents.⁶⁴ In particular, pentacyclic triterpenes of the lupan type can be found within the cork layers of the outer bark of white birches (*Betula alba* cortex) and include the biologically active substances betulinic acid, betulin, oleanolic acid, lupeol, and erythrodiol. Betulinic acid, one of the most studied substances within this class, promotes normal human keratinocytes differentiation, and exerts cytotoxic, antiproliferative, and apoptotic effects on tumor cells by directly acting on mitochondria. Moreover, it influences the activation of the transcription factor NF- κ B. Galenic preparations (ointment, oleogel) of triterpene extracts from birch bark, mainly containing betulinic acid, have been experimentally utilized in the treatment of AKs.⁶⁵ In these pilot studies no severe adverse events were observed; skin tolerance was excellent.

CONCLUSIONS

Several topical drugs are now available for the treatment of superficial forms of skin cancer. New molecules are under development, as are new formulations, new dosages and simpler therapeutic schedule of existing agents, which may ensure greater patient compliance.

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Topical pharmacotherapy for skin cancer

Part II. Clinical applications

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and identify topical skin cancer therapies that are appropriate for specific clinical indications.

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The purpose of the paper is to provide an in-depth, evidence-based analysis of the clinical use of topical treatments for skin cancer. A comprehensive review of topical drugs has been performed, including 5-fluorouracil, imiquimod, diclofenac, ingenol mebutate, retinoids, resiquimod, piroxicam, dobesilate, and betulinic acid. The evaluated studies were rated according to their level of evidence level (I-V), as indicated by recent guidelines for evidence-based medicine, *The Oxford 2011 Levels of Evidence*. Therapeutic response is generally related to tumor type, extent, and localization, and also to patient compliance. Careful patient selection is required in order to achieve the desired goal of complete tumor clearance. (J Am Acad Dermatol 2014;70:979.e1-12.)

Key words: actinic keratosis; basal cell carcinoma; Bowen disease; erythroplasia of Queyrat; lentigo maligna; melanoma; Paget disease; skin cancer; squamous cell carcinoma; topical treatment.

INTRODUCTION

The incidence of skin cancer is increasing worldwide, with >2 million cases diagnosed in the United States per year.¹ Surgical or invasive procedures represent the main approach, but noninvasive, tissue-sparing, topical self-administered treatments may be a highly desirable alternative, both in aged and unhealthy patients (who may be poor surgical candidates) and in relatively young subjects with lesions located on cosmetically sensitive areas and who wish to avoid disfiguring scars.²

The purpose of this review is to evaluate the effectiveness of topical treatments of skin cancer according to evidence-based medicine guidelines. The mechanism of action, formulations, indications, side effects, and contraindications of these drugs were analyzed in part I of this continuing medical education article.

All studies evaluating topical treatments for skin cancer published in the English literature between January 1960 and June 2013 were analyzed. To accomplish this, an electronic search was performed using the National Library of Medicine PubMed database of the National Institutes of Health and the Ovid MEDLINE database using the phrase "topical treatment" in combination with 1 of the following terms: "skin cancer," "actinic keratosis," "basal cell carcinoma," "squamous cell carcinoma," "Bowen disease," "erythroplasia of Queyrat," "Paget disease," and "melanoma." In addition, pertinent references not identified by search engines and retrieved from articles and books were also considered. All studies identified as relevant were analyzed, including metaanalyses, systematic reviews, clinical trials, controlled studies, and case reports. Evaluated studies were rated according to recent modified guidelines for evidence-based medicine, *The*

Abbreviations used:

5-FU:	5-fluorouracil
AK:	actinic keratosis
BCC:	basal cell carcinoma
BD:	Bowen disease
DHA:	diclofenac 3% gel in 2.5% hyaluronic acid
EPD:	extramammary Paget disease
EQ:	erythroplasia of Queyrat
IM:	ingenol mebutate
IQ:	imiquimod
LM:	lentigo maligna
RQ:	resiquimod
SC:	solar cheilosis

Oxford 2011 Levels of Evidence,³ as follows: level of evidence I, systematic review of randomized trials; II, randomized trial or observational study with dramatic effect; III, nonrandomized controlled cohort/follow-up study; IV, case series, case control studies, or historically controlled studies; and V, mechanism-based reasoning.

ACTINIC KERATOSES

Key points

- **In the management of multiple actinic keratoses, topical therapy should be preferred to more destructive and/or invasive treatments in consideration of the field effect, which allows treatment of both visible and subclinical lesions**
- **A Cochrane review concluded that, among field-directed treatments, 5-fluorouracil, imiquimod, diclofenac 3% gel in 2.5% hyaluronic acid, and ingenol mebutate showed similar efficacy with different adverse events and cosmetic outcomes, and more direct comparisons between these treatments are needed to determine the best efficacy profile**

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Actinic keratoses (AKs), also known as solar keratoses, are considered to be precancerous lesions by some authors and *in situ* squamous cell carcinomas (SCCs) by others.⁴ The real progression rate toward an invasive SCC, which has a metastatic risk of 0.5% to 3.3%, is unknown, varying from 0.025% to 20%. However, this inability to predict which AK will transform into an invasive SCC indicates that treatment of each visible AK is advisable.⁴ Treatment of AKs include lesion-directed (eg, cryosurgery, curettage and electrodesiccation, shave excision, and laser ablation) and field-directed therapies (eg, photodynamic therapy and topical pharmacotherapy).⁵ Of note, AKs represent the earliest clinically detectable cutaneous lesions of multifocal, preneoplastic areas of dysplastic keratinocytes that can extend beyond visible lesions. The use of topical agents to promote reversal of neoplastic transformation in surrounding tissue may provide a field effect on subclinical disease, and may contribute to the prevention of additional lesions in adjacent areas.⁵⁻⁸

5-Fluorouracil (5-FU) has been an established treatment for AKs since the pioneering work of Klein et al^{4,9-16} in the 1960s. It generally represents a standard treatment with which the efficacy of other topical treatments is compared.¹³ The best results are achieved with twice daily applications of the 5% concentration for 2 to 4 weeks.^{16,17} The efficacy of less frequent but more prolonged applications (once or twice per week for 6-7 weeks), or lower concentrations (0.5-1%) is unclear.^{15,17} In a literature review evaluating the efficacy of 5-FU cream 0.5% and 5% in treating multiple AKs of the face and scalp, complete clearance rates ranged from 16.7% to 57.8% and from 43% to 100%, respectively.¹⁸ A systematic review including 13 randomized, controlled trials (RCTs) evaluated both the short- and long-term efficacy of 5-FU at different dosing regimens, concluding that about one-half (49% with the 5% formulation and 34.8% with the 0.5% formulation) of patients can expect complete clearance, with an overall 80% reduction in lesion count. However, the authors concluded that the quality of the studies providing this evidence was poor.⁴ In addition, recurrences were frequently reported.¹⁹

Imiquimod (IQ) 5% cream applied 2 times per week for 16 weeks (schedule in the United States) was evaluated in a metaanalysis including 5 RCTs, and was found to achieve complete clearance in 50% of patients (compared to 5% of placebo) affected by AKs.²⁰ Another metaanalysis evaluated 4 RCTs in which IQ 5% was applied 3 times a week for up to 12 or 16 weeks (schedule in the European countries) in 3 studies and twice weekly for 16 weeks in 1 study: complete clinical clearance of AKs was observed in

57% to 84% of patients (compared to 0-2% of patients treated with placebo) and histologic clearance was observed in 45% to 48% of patients (compared to 3-7% with placebo).²¹ The authors noticed that the number of AKs generally increased during the initial phases of treatment as a result of the appearance of subclinical ones because of the field effect. With regard to the long-term efficacy of the IQ 5% formulation, 1 RCT in which complete clearance was reported in 84% of subjects at 12 weeks has shown that, of these, 80% were lesion-free after 24 months.²² Regarding the lower dosages of IQ, 479 patients were randomized to receive IQ 3.75% cream or IQ 2.5% cream or placebo for two 2-week cycles.²³ After 8 weeks, complete and partial clearance ($\geq 75\%$ lesion reduction) rates were 35.6% and 59.4% for IQ 3.75%, 30.6% and 48.1% for IQ 2.5%, and 6.3% and 22.6% for placebo; median reductions in lesion counts from baseline were 81.8%, 71.8%, and 25%, respectively.

Diclofenac 3% gel in 2.5% hyaluronic acid (DHA) is another feasible treatment for AKs, and several studies are available.^{17,24,25} In 2 RCTs, a complete resolution rate was achieved in 33% and 50% of 48 and 120 patients, respectively, after 60 and 90 days of treatment with twice-daily applications.^{24,25} A meta-analysis of 3 studies with a total of 364 patients revealed complete remission in 39.1% of patients.²⁶ Treatment duration does not seem to influence response rates; a multicenter, randomized open-label study of 418 patients revealed complete clearance in 40% and 45% of subjects after 3 and 6 months, respectively.²⁷

Ingenol mebutate (IM) has shown to be effective for the treatment of AKs with a short treatment regimen.²⁸⁻³⁰ In 4 multicenter, randomized, double-blind studies, patients with AKs were assigned to receive IM gel (0.015% for face and scalp and 0.05% for trunk and extremities) or placebo once daily for 3 (face or scalp) or 2 (trunk or extremities) consecutive days.²⁸ After 57 days, the rate of complete clearance was higher with IM than placebo (42.2% vs 3.7% for face and scalp lesions; 34.1% vs 4.7% for trunk and extremity lesions). In a long-term follow-up study, the sustained lesion reduction rates after 12 months, compared to baseline, were 87.2% for the face or scalp and 86.8% for the trunk or extremities, with no safety concerns.²⁹

Topical retinoids, although not approved by the US Food and Drug Administration (FDA), have shown some efficacy in the treatment of facial AKs.^{14,17} In a multicenter study, 1265 patients were treated with tretinoin 0.05% or 0.1% cream or with a vehicle applied twice daily for 15 months. The patients treated with the 0.1% formulation achieved

a 73% reduction in the total number of lesions.³¹ Another double-blind, parallel-group study of 100 patients found that 66% of subjects treated with 0.1% isotretinoin twice daily for 24 weeks achieved a >30% reduction in lesion count.³² Finally, in a prospective, controlled study, 90 subjects with AKs and photodamage were randomized to either adapalene gel (0.1% or 0.3%) or vehicle, once daily for 4 weeks, followed by twice-daily application up to 9 months.³³ Overall, 62% and 66% of subjects in the adapalene gel 0.1% and 0.3% groups, respectively, were considered to have shown clear, marked, or moderate improvement in AKs.

Emerging therapies

A phase II dose-ranging study on 132 patients reported the successful use of resiquimod (RQ) gel at different concentrations (0.01%, 0.03%, 0.06%, or 0.1%) for facial and balding scalp AKs.³⁴ RQ was applied 3 times a week for 1 or 2 courses of 4 weeks, with complete clearance varying from 40% to 74.2% after 1 course and from 77.1% to 90.3% after 2 courses. The efficacy in reducing the number of AKs was similar in all groups, but lower concentrations were better tolerated.^{19,34} Another compound, piroxicam 1% gel, applied twice daily for 90 days on 31 AKs, has shown in a preliminary open-label study complete clinical regression in 48% of lesions.³⁵ A recent preliminary open-label study on 30 patients with potassium dobesilate 5% cream applied twice daily for 16 weeks revealed complete regression in 70% of patients and a partial response (at least 75% reduction of lesions) in 20% of patients.³⁶ Finally, in a prospective, randomized pilot study of 45 patients, the twice-daily application of betulin-based oleogel for 3 months achieved 64% complete AKs clearing and 86% extensive response (>75% clearing).³⁷

Comparative studies

In a metaanalysis comparing IQ with 5-FU, a relatively higher efficacy of IQ 5% compared to 5-FU (0.5%, 1%, and 5%) has been noted for AKs located on the face or scalp: the efficacy rate was 70% for IQ compared to 52% for 5-FU.³⁸ With regard to DHA compared to IQ, a randomized, open-label, 12-week study on 49 subjects revealed a complete response in 12% of subjects treated with once daily applications of DHA versus 22% of subjects treated with IQ 5% cream 3 times per week.³⁹ Another single-center, open-label, evaluator-blinded study on DHA (twice daily for 12 weeks), IQ 5% cream (twice per week for 16 weeks) and placebo (twice daily for 12 weeks) in 61 patients showed complete clearance rates of 19.1%, 20%, and 0%, respectively, at the end of treatment, and of 14.3%, 45%, and 0% at the 24-week

follow-up.⁴⁰ In a recent randomized, double-blind, multicenter trial, 470 patients with AKs on the face/forehead or bald scalp received 5-FU 0.5% in combination with salicylic acid (SA) 10% solution or its vehicle once daily, or DHA twice daily for a maximum of 12 weeks.⁴¹ The combination 5-FU/SA was more effective, with a complete clinical clearance of 55.4% compared to 32% of DHA and 15.1% of vehicle.

Comments

Several topical compounds are effective for the treatment of AKs. In particular, the efficacy and safety of 5-FU, IQ, DHA, and IM have been shown by well-conducted randomized trials. However, some important issues need to be addressed. The first concern is the delineation of which patients will gain the greatest benefit from topical treatment and which lesions are most (or least) likely to be cured. In this regard, there is a lack of good quality evidence.⁴ Generally, single lesions are best treated with lesion-directed therapies, and topical treatments may be considered in case of lesions on the face, ears, and nose, or in cases of existing contraindications to invasive approaches. Topical therapy should also be considered in case of multiple lesions on the entire sun-damaged area in consideration of the field-cancerization phenomenon. Hyperkeratotic lesions are less amenable to topical therapy, unless associated with a keratolytic agent. Patient compliance and adherence to home therapy are crucial.

Another issue is which of the different molecules and formulations are the most suitable for each individual patient. Again, there is insufficient evidence to enable clinicians to make informed choices.⁴ Comparison among studies is often difficult, because different evaluation criteria of drug efficacies have been used, such as absolute and proportional changes in lesion counts per patient, changes in total lesion count, change in lesional area, complete response rate (100% clearance), and partial response rate ($\geq 75\%$ clearance).⁴ A Cochrane review concluded that among field-directed treatments, 5-FU, IQ, DHA, and IM showed similar efficacies with different adverse events and cosmetic outcomes, and more direct comparisons between these treatments are needed to determine the best efficacy profile.⁴² For this reason, it is difficult to create guidelines. At the moment, the choice depends on several factors related to the type, number, and location of AKs, the patient's conditions and compliance and, nevertheless, to the physician's familiarity with the drug. Finally, the availability and cost of the drugs, which may vary among different countries, are also important and may influence therapeutic management.

IQ 5% cream has undoubtedly the best evidence supporting its efficacy in the treatment of AKs. At different dosing regimens, both clinical clearance at the end of the treatment and sustained long-term clearance rates are high. An explanation for this is that the induction of specific memory T cells by IQ may produce continuing immune surveillance that may limit recurrences. A limitation of IQ 5% is represented by the frequent and sometimes significant side effects (see the part I of this continuing medical education article) that may reduce compliance and restrict its use to a small surface area. Lower percentages of IQ (3.75% and 2.5%) have been marketed to minimize this issue, but their efficacy appears to be reduced.

5-FU has been used for the longest period of time for the treatment of AKs, and a majority of physicians have the greatest amount of confidence with its use. It is considered a low-cost and effective treatment, especially the 5% formulation, although high-quality trials have never been performed and the recurrence rate is high. As for IQ, its use is limited by the nearly constant onset of local skin reactions.

With regard to DHA, its efficacy appears to be lower than that of other topical treatments. However, an advantage of this drug is the low degree of local skin reactions, so it may be used with more confidence in larger areas, in sensitive patients, and around the eyes and mouth.

The most recently marketed treatment for AKs, IM, has shown good clinical efficacy, similar to those of other topical treatments, although comparative studies have not been performed and clinical experience is limited. Its great advantage is represented by its short time of treatment, consisting of 1 application for 2 or 3 consecutive days, that enables patient adherence to therapy. A current limitation of IM is that it can be applied with confidence on a single skin area of up to 25 cm²; additional studies are needed to assess the risks and benefits of treating larger areas.

The value of topical retinoids for the treatment of AKs is less evident because the number of studies supporting their efficacy on AKs is small. In addition, these drugs are not approved by the FDA for this indication, so they are often not prescribed unless in the context of a photoaging treatment.

BASAL CELL CARCINOMA

Key points

- **5-Fluorouracil 5% and imiquimod 5% represent effective treatments for small superficial basal cell carcinomas**

- **With regard to imiquimod 5%, 5 applications per week is the recommended regimen because it provides the best compromise between clinical efficacy and safety with minimal side effects**
- **Imiquimod 5% can be an alternative treatment for small nodular basal cell carcinomas in patients who are poor candidates for surgical treatment**

Basal cell carcinoma (BCC) represents the most common human malignant neoplasm that rarely metastasizes but, if neglected, is more likely to be locally aggressive, destroying underlying tissues.⁴³ Small BCCs can be effectively treated with simple excision, cryosurgery, and curettage and electrodesiccation. The appropriate use criteria for microscopically controlled excision (Mohs micrographic surgery) of BCCs have been recently approved and are based on tumor type, size, and localization and patient characteristics.⁴⁴ Photodynamic therapy and topical pharmacotherapy may represent useful alternative options.

5-FU 5% cream is approved for the treatment of superficial BCCs, but few studies support its efficacy.⁴⁵⁻⁴⁷ A single-arm evaluation of 31 superficial BCCs treated with 5-FU 5% cream twice a day for up to 8 to 12 weeks revealed complete histologic clearance in 90% of lesions.⁴⁷ In another pilot study, 13 subjects with 17 biopsy-proven superficial BCCs were randomized to receive, twice daily, either the classic 5-FU 5% in a petrolatum-base (PB) or 5-FU 5% in a phosphatidyl choline (PC) vehicle.⁴⁶ After 4 weeks, lesions treated with the PC formulation had a 90% resolution rate, both clinical and histologic, compared to 57% of those treated with PB vehicle. Finally, the efficacy of 5-FU in nodular BCCs is low, because very few cases reported its successful use.^{48,49}

IQ 5% cream is effective in the treatment of small superficial BCCs (maximum size: 2 cm in diameter), as shown by several RCTs and 1 systematic review.⁵⁰ In a RCT including 128 patients treated for 12 weeks with twice daily, once daily, 5 days per week, and 3 days per week applications, histologic clearance rates were 100%, 87%, 81%, and 52%, respectively.⁵¹ Two long-term prospective studies of 182 and 169 patients showed complete clearance rates after a 5-year follow-up of 77.9% and 80.4%, respectively.^{52,53} Multiple studies evaluated IQ 5% for small nodular BCCs (maximum size: 1.5 cm in diameter). Two phase II randomized studies were conducted on 99 patients for 6 weeks and on 92 patients for 12 weeks to evaluate 4 IQ 5% cream dosing regimens: once daily dosing resulted in the highest clinical and

histologic clearance rate (71% and 76% in the 2 studies, respectively).⁵⁴ Finally, some case reports and small series have described positive responses in large superficial BCCs⁵⁵ and multiple BCCs as observed in basal cell nevus syndrome (Gorlin syndrome).^{56,57}

IM represents a promising short-course treatment for BCCs.^{1,58} In a phase II study, 60 patients with histologically proven superficial BCCs were randomized to receive 2 applications of IM gel (at days 1 and 2 or 1 and 8) at different dosing (0.0025%, 0.01%, or 0.05%) or vehicle gel.⁵⁹ At the end of the treatment, efficacy was found to be dose-related, with best results (clearance of 71% of lesions) achieved with the 0.05% concentration.

In a clinical study on 20 subjects with superficial and nodular BCCs, tazarotene 0.1% gel, applied once a day up to 8 months produced a complete response, defined as the clinical disappearance of BCCs, in 53% of cases (11 of 13 superficial and 5 of 17 nodular lesions).⁶⁰

Finally, in 2 case reports, topical formulations containing 2.5% dobesilate, applied twice daily for 4 weeks, resulted in complete resolution of 1 nodular and 2 infiltrative BCCs.^{61,62}

Comparative studies

A recent multicenter RCT assessed the effectiveness of photodynamic therapy using methylaminolevulinate (2 sessions with an interval of 1 week) compared with IQ 5% cream (once daily, 6 times a week for 6 weeks) or 5-FU 5% cream (twice daily for 4 weeks) in 601 patients with superficial BCCs.⁶³ The proportion of patients who were tumor-free at both 3 and 12 months of follow-up was 72.8% for photodynamic therapy, 83.4% for IQ, and 80.1% for 5-FU.

Comments

BCC is the type of invasive skin cancer that is most likely to benefit from the use of topical treatments. The identification of eligible types of BCC is crucial. Response to therapy must be carefully monitored and, because clinical appearance after treatment cannot definitely exclude the presence of residual tumors, a close follow-up, preferably with the support of dermoscopy, is mandatory.^{64,65} The efficacy of IQ 5% in superficial BCCs is well-demonstrated (level of evidence: I): the 5 application per week regimen is recommended because it provides the best compromise between clinical efficacy (about 80% of clearance rate, confirmed in long-term studies) and safety, with fewer side effects. Generally, it is applied daily from Monday to Friday with a 2-day rest period given over weekends.¹³

Clinical trials usually refer to 2 cm maximum diameter, but, according to physician experience, larger superficial BCCs may also benefit from this therapy. The efficacy on small nodular BCCs is lower (about 70% of clearance rate); in this case, IQ may represent an alternative treatment in those patients who are unable to undergo surgical treatment.

5-FU 5% cream was the first nonsurgical agent approved by the FDA for the treatment of superficial BCCs. However, new, well-designed trials on 5-FU and data on recurrence rates and long term follow-up are scant.

OTHER INDICATIONS

Key points

- In the treatment of Bowen disease, 5-fluorouracil 5% and imiquimod 5% may be considered as alternatives to surgery; in particular, imiquimod has a level of evidence II
- The use of topical pharmacotherapy in erythroplasia of Queyrat, extramammary Paget disease, lentigo maligna, and melanoma metastases is currently limited to level of evidence IV; additional trials are necessary to validate its efficacy on larger series of patients

Solar cheilosis

Solar cheilosis (SC), also known as actinic cheilitis, is basically AK of the lower lip. The treatment of SC with 5-FU, IQ, and DHA⁶⁶⁻⁶⁸ has been reviewed and a level of evidence judgment rendered⁶⁹ (Table 1). A standard treatment for SC is 5-FU 5% applied 2 to 3 times daily for 9 to 15 days. However, it may not resolve SC histologically, despite clinical remission.⁶⁹

Bowen disease

This form of *in situ* SCC clinically appears as a long-standing, oval, erythematous and scaling plaque.⁷⁰ If untreated, 3% to 26% of cases may develop invasive SCC. Therapeutic options include surgical excision, cryosurgery, curettage and electrodesiccation, laser ablation, photodynamic therapy, and topical pharmacotherapy.

In an open-label study of 26 biopsy-confirmed cases of BD treated with topical 5-FU 5% twice daily for up to 9 weeks, 92% of subjects reported complete clearance with an average follow-up duration of 55 months.⁷¹ One randomized trial compared the efficacy, safety, and cosmetic outcome of 5-FU 5% cream applied once a day for one or two 4-week cycles compared to photodynamic therapy with 20% 5-aminolaevulinic acid.⁷² The clearance rates were

Table I. Trials on topical drugs for skin cancer treatment and their level of evidence*

Drug	AK	SC	BCC		BD	EQ	EPD	LM	MM
			Superficial	Nodular					
5-fluorouracil	I	II	II	IV	IV	IV	IV	—	IV
Imiquimod	I	IV	I	II	II	IV	IV	IV	IV
Diclofenac	II	IV	—	—	IV	—	—	—	—
Ingenol mebutate	II	—	II	—	—	—	—	—	—
Retinoids	II	—	IV	IV	—	—	—	IV	—
Resiquimod ^t	IV	—	—	—	—	—	—	—	—
Piroxicam	IV	—	—	—	—	—	—	—	—
Dobesilate ^t	IV	—	IV	IV	—	—	—	—	—
Betulinic acid ^t	IV	—	—	—	—	—	—	—	—

AK, Actinic keratosis; BCC, basal cell carcinoma; BD, Bowen disease; EPD, extramammary Paget disease; EQ, erythroplasia of Queyrat; LM, lentigo maligna; MM, melanoma metastases; SC, solar cheilosis.

*Levels of evidence, according to the Oxford Centre for Evidence Based Medicine³: I, systematic review of randomized trials; II, randomized trial or observational study with dramatic effect; III, nonrandomized controlled cohort/follow-up study; IV, case series, case-control studies, or historically controlled studies; and V, mechanism-based reasoning.

^tCommercially unavailable.

67% versus 88% at the end of treatment and 48% versus 82% at 12 months of follow-up. With regard to IQ 5% cream, 1 RCT concluded that 73% of 31 patients treated with once-daily application for 16 weeks had both clinical and histologic resolution, with no relapse during a 9-month follow-up period.⁷³ These results have been confirmed by several non-RCTs and case reports.⁷⁴ Finally, in some isolated cases, DHA applied once or twice a day for 8 to 12 weeks led to clinical and histologic clearance.^{75,76}

In conclusion, 5-FU and IQ may be considered as alternatives to surgery, especially for large-sized BD.

Erythroplasia of Queyrat

Erythroplasia of Queyrat (EQ) represents an *in situ* SCC of the male genital mucosa.⁷⁷ The etiology is not well known, but chronic irritation is believed to play an important role. It is rare, and preferentially occurs in uncircumcised men as a velvety, bright red, sharply demarcated patch or plaque on the distal penis (ie, the glans, corona, sulcus, and prepuce). Because EQ may evolve into invasive SCC, surgical removal of the cancer is a standard approach, although it is associated with considerable mental distress.⁷⁸ Few case reports showed favorable results using topical 5-FU⁷⁹ and IQ 5%⁸⁰⁻⁸²; the latter has been successfully used from 3 to 7 times a week for 4 to 24 weeks. Patients should be strictly followed up because the rate of recurrence is high.⁷⁸

Extramammary Paget disease

Extramammary Paget disease (EPD) is an uncommon adenocarcinoma of apocrine gland-bearing

skin. Clinically, it appears as a sharply demarcated, erythematous scaling plaque mainly occurring in the anogenital area. The standard treatment for EPD is wide local excision or Mohs micrographic surgery.⁸³ Some case reports suggest that IQ 5% may be useful for female and male EPD (daily application or 2-3 times a week for a minimum of 8-16 weeks) in patients who are not candidates to surgery.⁸⁴⁻⁸⁷ One recent study, however, reported therapeutic failure in 2 cases.⁸⁸ IQ has also been proposed as neoadjuvant therapy before surgery, allowing for a reduction in tumor size, making the subsequent surgical excision easier.⁸⁹ In few case reports, 5-FU has been used for the treatment of EPD alone or in combination therapy.⁹⁰⁻⁹² In conclusion, despite an apparently successful course, the patient must be carefully monitored.

Lentigo maligna

The progression rate of lentigo maligna (LM)—an *in situ* melanoma—to invasive melanoma is slow, with an estimated lifetime risk of 5%.⁹³ Wide local excision represents the treatment of choice, but this may be difficult and is not always feasible because of the patient's age and/or general medical conditions. Several uncontrolled studies and case reports evaluated the efficacy of IQ 5% cream in the treatment of LM.⁹⁴⁻¹⁰² Dosage varies from 3 times weekly to daily, with duration of 2 weeks to 7 months.¹⁰¹ Clinical response rates ranged from 66% to 100%. Studies that evaluated the histologic response to IQ after total resection of the treated area revealed complete clearance in 53% to 75% of cases.^{99,102} However, as suggested, the duration of follow-up for most of these studies is 12 months or

less, inadequate to prove therapeutic efficacy in LM, which is characterized by a slow radial growth phase.¹⁰³

Regarding other topical treatments for LM, 1 case report on 2 elderly subjects with facial LM showed both clinical and histologic complete regression after once-daily application of tazarotene 0.1% gel for 6 to 8 months.¹⁰⁴ These results were not confirmed by other studies.

In conclusion, a noninvasive treatment is desirable in LM. The results obtained with IQ are appealing. However, this approach is risky because LM may have a hidden invasive component. A review has shown that if the biopsy represents only a portion of the lesion, there is a 22% risk that, after an initial diagnosis of LM, an invasive component will subsequently be revealed when the entire lesion is removed and histologically examined.¹⁰³ Some cases of LM progressing to invasive melanoma after treatment with IQ have been reported¹⁰⁵⁻¹⁰⁷; it is likely that the invasive component was present before IQ treatment, but not detected on initial biopsy.¹⁰³ In any case, a risk exists that the topical therapy may conceal invasive disease or the development of invasive disease. Because the consequences of such risks are life-threatening, IQ must be used with considerable caution in the treatment of LM and then only in selected cases.¹⁰³ A long-term follow-up and multiple posttreatment biopsies are suggested, even in the absence of clinical evidence of LM.

Melanoma metastases

Although metastatic melanoma has a poor prognosis, the treatment of cutaneous metastases may be beneficial for palliation. Since the report of successful treatment of cutaneous metastases in 2000,¹⁰⁸ the off-label use of topical IQ has been proposed as an alternative treatment to surgery and as an adjunctive modality after surgical excision, either alone or in combination with other systemic modalities.^{109,110} In a case report, IQ 5% has been successfully used in combination with topical 5-FU.¹¹¹

CONCLUSIONS

Although the standard approach to cure skin cancer remains surgical, topical pharmacotherapy represents an appropriate alternative to consider. There are a considerable number of evidence-based medicine studies with evidence levels I to II (Table I) that confirm the efficacy of topical pharmacotherapy in AKs,^{4,20,24,25,28,33} SC,⁶⁹ BD,⁷³ and in small superficial BCCs.^{50,51,59,63} Of note, most studies on AKs indicate that topical therapy may be preferred to

destructive and/or invasive treatments in case of multiple lesions, because of the field effect phenomenon, which highlights both visible and subclinical lesions.

Factors that favor the use of topical pharmacotherapy include extensive, multifocal, multiple tumors, indistinct lesion boundaries, localization in cosmetically sensitive or difficult to treat areas, and a history of hypertrophic and/or keloidal scarring. Additional indications include patients in whom cumulative surgical procedures may result in functional or cosmetic disfigurement, the presence of surgical risk factors (ie, age and comorbidities) and patient preference to avoid invasive procedures. When considering a topical approach, careful patient selection is required in order to achieve the desired goal, which is complete tumor clearance, keeping in mind that therapeutic response is related both to tumor type, extension and localization, and to patient compliance. Before and after treatment, histologic confirmation is pivotal, as is careful posttreatment follow-up. Regarding the cost of treatment of topical pharmacotherapy, it appears to compare favorably to that of surgery.¹¹²

The use of topical pharmacotherapy for EQ, EPD, LM, and melanoma metastases is currently limited to level of evidence IV (Table I); additional trials are necessary to validate its efficacy on larger series of patients.

In conclusion, many factors must be taken in account when considering a treatment of nonmelanoma skin cancer with topical agents, including approved indications, efficacy, side effects, physician preference, patient compliance, and cost.¹¹² Overall, among the examined topical treatments, 5-FU represents the drug with the best cost-benefit ratio. IQ is the most versatile agent for which exists firm literature support and sufficiently long clinical use. DHA, indicated only for the treatment of AKs, presents the lowest degree of local skin reactions. Because of its efficacy and short course of treatment (2-3 days), IM represents the more promising agent, although studies on larger series of patients are necessary.

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Proactive infectious disease approach to dermatologic patients who are taking tumor necrosis factor–alfa antagonists

Part I. Risks associated with tumor necrosis factor–alfa antagonists

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Learning Objectives

After completing this learning activity, participants should be able to describe the many infectious risks potentially associated with the use of biologic therapy for the

treatment of psoriasis and obtain appropriate historical data specific to the risks of various infectious entities.

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Tumor necrosis factor–alfa levels are linked to disease severity in patients with inflammatory conditions, such as psoriasis. Inhibitors of this cytokine are commonly used with significant success in the treatment of such inflammatory disorders. Their use, however, can be plagued by infectious complications. An awareness of potential infections associated with these therapies is critical in order to maximize preventive efforts both before and during therapy. This review provides a guide for dermatologists caring for patients in need of this type of biologic therapy to preemptively address the infectious risks. Part I of this continuing medical education article reviews background information on the various infectious risks associated with tumor necrosis factor inhibitor therapy and appropriate historical data to obtain in the context of pretherapy evaluations. (J Am Acad Dermatol 2014;71:1.e1-8.)

Key words: biologic therapy; endemic mycoses; opportunistic infection; psoriasis; tuberculosis; tumor necrosis factor.

INTRODUCTION

Tumor necrosis factor–alfa (TNF α) antagonists have revolutionized our approach to patients with life-altering inflammatory conditions, such as inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Levels of TNF α are increased in both the skin and serum of patients with psoriasis, correlate with disease severity, and return to normal after successful treatment.¹

These therapies can be highly effective, but they can also be associated with significant infectious complications. Although relatively common illnesses predominate, such as upper respiratory tract infections, there are multiple infectious associations with pathogens, including bacteria, mycobacteria, fungi, viruses, and parasites. The tuberculosis risk for patients receiving tumor necrosis factor inhibitors (TNFIs) has prompted the addition of black box warnings to the labels of these agents.

The existing literature to guide dermatologists in their evaluation of patients who are beginning TNFI therapy is not comprehensive. Much of this relates to the fact that the quality of evidence quantifying infectious risk is limited, especially for infectious agents that are unusual causes of illness in normal hosts. Many pathogenic associations with these medications are reported in postmarketing case reports and in other clinical disease states, such as rheumatoid arthritis and inflammatory bowel disease. It is important that the clinician be cognizant of the potential for infectious complications of TNFIs before therapy begins so that appropriate preventive measures may be undertaken to prevent future morbidity and mortality. We provide a framework

for the dermatologist to address the many potential infection-related concerns before the initiation of biologic therapy.

POTENTIAL PATHOGENS IN TUMOR NECROSIS FACTOR INHIBITOR PATIENTS: “WHAT I NEED TO KNOW”

Key points

- Dermatologists who are considering treating patients with severe psoriasis with tumor necrosis factor inhibitor therapy may not be familiar with the complex and diverse potential infectious complications associated with such therapy
- Knowledge of the specific risk factors associated with such entities results in more comprehensive pretherapeutic evaluation and may result in reduced morbidity associated with these therapies by informing preventive strategies
- A comprehensive baseline history directed at specific epidemiologic and exposure risks is critical for minimizing infectious complications associated with tumor necrosis factor inhibitor therapy

TNF α plays a critical role in the clearance of intracellular bacterial pathogens, such as *Streptococcus pneumoniae* and *Listeria monocytogenes*.³ Patients receiving TNFI therapy therefore have a significantly increased risk of developing a serious infection with such pathogens. Infections with typical organisms have been described, such as streptococcal and staphylococcal species, including invasive, severe manifestations, such as necrotizing fasciitis.^{3,4}

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Infection with atypical bacterial pathogens, such as *Salmonella enteritidis* and *Legionella pneumophila*, may be related to specific exposures, as discussed below.

Some of the more common pathogens associated with TNFI therapy are *Mycobacterium tuberculosis* and the endemic mycoses. *M tuberculosis* infects one-third of the world's population and causes 9 million new cases of tuberculosis and approximately 2 million deaths annually. The tuberculosis rate in foreign-born persons is 10 times higher than that in individuals born in the United States, and foreign-born persons now account for most of the reported cases in the United States. This is likely because of increasing immigration from countries with a high prevalence of tuberculosis—especially Mexico, the Philippines, Vietnam, India, and China, which account for >50% of foreign-born tuberculosis cases. Overall, developing nations are the most impacted with tuberculosis, and 12 countries account for 70% of all cases.²

M tuberculosis is an aerobic, non-spore-forming, nonmotile bacillus that is primarily spread by the inhalation of droplet nuclei from a person with pulmonary involvement after becoming aerosolized by coughing, sneezing, or talking.² Most cases of tuberculosis are localized to the lungs, but approximately 15% to 20% of infections are extrapulmonary, most often affecting the lymph nodes and solid organs.³ The species *M tuberculosis* within the *M tuberculosis* complex causes the vast majority of human tuberculosis.

Coccidioidomycosis is limited to the western hemisphere and is commonly found in the southwestern United States, including parts of California, Arizona, Nevada, New Mexico, and Texas (Fig 1). It is also found in northern Mexico and parts of Central and South America, such as Argentina and Paraguay, where the climate is similar to the locations in the United States. Infection with *Coccidioides immitis*, a dimorphic fungus, is acquired after inhalation of arthroconidia that are present in soil. Disease may develop after primary infection, and in normal hosts is usually subclinical or mild. Reactivation of dormant disease may also occur, and is more likely in immunodeficient persons. Primary clinical manifestations include acute respiratory infections, but extrapulmonary manifestations can occur in the skin, lymph nodes, bone, joints, or central nervous system.^{3,5}

Histoplasmosis is an endemic mycosis found commonly in the United States. *Histoplasma capsulatum* is concentrated in the states bordering the Mississippi and Ohio River valleys, and focused pockets exist in multiple eastern states. It is also found throughout North and Central America and in

many places around the world (Fig 1).⁵ Caused by the dimorphic fungus *H capsulatum*, it is acquired through the inhalation of microconidia (spores) and other fungal elements in the soil. Clinical disease may be primary, reactivated, or reinfection. Most patients with primary infection remain asymptomatic. The most common clinical presentation is pneumonia. The organism can also disseminate to the bones, joints, kidneys, endovascular sites, and the central nervous system (CNS).^{3,6,7}

Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*. *B dermatitidis* is found in the Mississippi and Ohio River valleys, parts of the United States and Canada near the Great Lakes, and the St Lawrence Seaway, as well as certain areas of Africa (Fig 1).⁸ Blastomycosis can be a subclinical illness, but it may present with progressive disease with either pulmonary or extrapulmonary involvement. Lung involvement may mimic bacterial pneumonia, although chronic presentations do exist. The skin is a common site of extrapulmonary disease, followed by bone, prostate, and CNS involvement.⁹

Chronic hepatitis B infection may be exacerbated by TNFI therapy.^{10,11} Hepatitis B is a DNA virus that affects >350 million people worldwide. Uncontrolled chronic hepatitis B infection can lead to complications, such as cirrhosis and hepatocellular carcinoma. It is endemic to certain regions of the world, and transmission often occurs at birth in these areas. It can also be readily transmitted by contact with infected bodily fluids, such as blood.¹²

Other bloodborne pathogens that can be associated with TNFI therapy include hepatitis C virus and HIV. These viruses can be transmitted to health care workers in a similar way to hepatitis B and via exposure to bodily fluids through unprotected sex or contaminated needles. Hepatitis C is an RNA virus that infects up to 2% of the US population and can lead to cirrhosis and hepatocellular carcinoma. The effect of TNFI therapy in patients with hepatitis C is unclear, but it has been theorized that it may be less concerning than in hepatitis B, and may even lead to improved outcomes.¹⁰

HIV is a retrovirus responsible for significant global morbidity and mortality. It causes immunosuppression via infection and destruction of immunoregulatory T cells, resulting in opportunistic infections. There has been general concern regarding the use of TNFI therapy in patients with HIV infection given the additional immunosuppression in an already compromised population. Although there are limited data regarding the safety of TNFI therapy in HIV-infected individuals, it appears to be relatively well-tolerated in select patients.^{10,13}

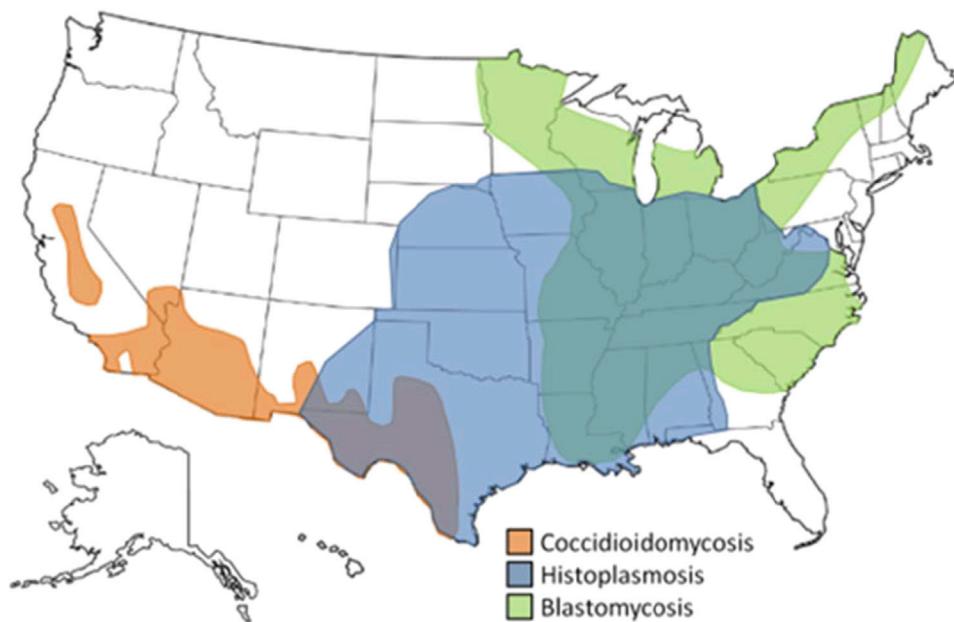


Fig 1. Areas of endemicity in the United States for coccidioidomycosis (orange), histoplasmosis (blue), and blastomycosis (green).

Because TNF is critical in the control of viral infection, it has been theorized that its blockade with TNFI therapy may increase the risk of acute or reactivation of other viral infections, such as herpesviruses, Epstein–Barr virus (EBV), cytomegalovirus (CMV), and varicella zoster virus (VZV).¹⁴ Cases of both primary and reactivation/disseminated CMV infection, including retinitis and colitis, have been reported in the literature in patients who are undergoing TNFI therapy, although the majority of these cases were either inflammatory bowel disease or arthritis.^{14,15}

Leishmaniasis is one example of a rarer infection that has been associated with the use of TNFIs and a history of travel to endemic regions. Leishmaniasis is caused by a protozoan hemoflagellate transmitted by the bite of a sandfly. There are a variety of disease manifestations, including skin, mucous membrane, or even internal organ involvement, which depends on the host's immunity and particular infecting species. In recent reports, most cases of visceral leishmaniasis occur in 6 countries: India, Bangladesh, Sudan, South Sudan, Brazil, and Ethiopia. Cutaneous leishmaniasis has a larger endemic area and is primarily found in 3 areas: the Americas, the Mediterranean, and western Asia from the Middle East to Central Asia.¹⁶ Recently, cases of opportunistic leishmaniasis in patients treated with TNFI therapy in Europe have been reported.^{17,18}

There have also been case reports describing infections of *Strongyloides stercoralis* associated with TNFI therapy.^{19,20} *S. stercoralis* is an intestinal

nematode that is acquired from skin contact with contaminated soil that is found in many tropical and subtropical areas, including Africa, Southeast Asia, Latin America, and parts of the southeastern United States. This organism can cause acute or chronic infections with primarily gastrointestinal, cutaneous, or pulmonary manifestations. A hyperinfection process can take place in patients with impaired immune function, where there is a rapid increase in parasite burden and dissemination to areas, such as the CNS, that are traditionally unaffected. This phenomenon can lead to complications, including sepsis, pneumonia, and meningitis.²¹

Other uncommon pathogens have been reported in patients receiving TNFI therapy. Of particular note, atypical bacteria found in soil, such as nocardia species and nontuberculous mycobacterial species (eg, *Mycobacterium avium*, *Mycobacterium terrae*, *Mycobacterium chelonae*, and *Mycobacterium marinum*) that may be inhaled or contaminate cutaneous injuries are important considerations.¹⁵

TAKING A HISTORY: “WHAT TO ASK FROM AN INFECTIOUS DISEASE PERSPECTIVE”

A complete history should be performed during a patient encounter before the initiation of TNFI therapy. Given the risks, this should include a review of the indications for therapy and whether the patient has been recently ill or is experiencing symptoms that are possibly consistent with an active infectious process. There are a myriad of pathogens

that can cause common or confusing symptoms; taking a thorough travel, social, and exposure history may provide the only clues as to the causative agent. Once TNFI therapy is considered, current or future infectious risks may be identified by a complete exposure history. In addition to a standard medical history, the patient should be questioned regarding a history of infections—even those that may have occurred in childhood and those of household members. Importantly, the clinician should elicit an accurate childhood vaccination history and adult vaccinations and international travel–related vaccinations.

Travel history and plans

Obtaining a detailed travel history is one of the most important components of an effective infectious disease exposure history. It is important to obtain information regarding patients' most recent travel experiences and those in the more remote past, including areas of prolonged residence. Future travel plans must be explored. Exposure to TNFI therapy may increase the risk of acquiring infections that may be acquired via travel or residence in certain endemic areas.

Occupation

Because the risk of infection with endemic mycoses in the setting of TNFI use is increased and these dimorphic fungi are present in soil, patients whose occupations bring them into contact with or during which they disturb the soil may be at risk. This may include activities such as farming, soil excavation, construction, or demolition.⁷

Health care workers may also be at increased risk for infectious complications of TNFI therapy by virtue of their interaction with patients harboring communicable diseases. One example is tuberculosis. Health care workers are more likely to encounter or care for patients with active tuberculosis. In the health care worker who is undergoing TNFI therapy, this is especially concerning. Bloodborne pathogens, such as hepatitis B and C and HIV, also present a concern in this setting.

Another theoretical occupational infection concern is *L pneumophila*, a Gram-negative bacillus acquired from an aerosolized water source. Patients are exposed through the inhalational route after having contact with water fountains, air conditioners, or cooling towers that are colonized with these bacteria. Patients undergoing TNFI therapy in occupations in these settings may be at an increased risk of infection.^{3,22}

Hobbies and leisure activities

Some hobbies or leisure activities may overlap with pathogens found in occupational activities, although the route of exposure may differ. For example, histoplasmosis can be associated with activities like spelunking (cave exploration) given the association of soil contaminated with bird or bat feces serving as nidus for the growth of this fungus.^{6,7} Other activities that disturb the soil as mentioned above can lead to a risk of fungal infection. There have been reports of infections, such as sporotrichosis, occurring in patients who are undergoing TNFI therapy.²³ *Sporothrix schenckii* is another fungal pathogen that can reside in the soil and is commonly associated with farming or gardening. This disease classically presents with lymphangitis or pneumonitis.²⁴

Diet

A person's diet may occasionally be the source of infection, such as the consumption of raw or undercooked meats or unpasteurized dairy products. One of the better-described associations of foodborne illness and TNFI therapy is listeriosis.^{25,26} *Listeria monocytogenes* is a Gram-positive intracellular bacterium that usually affects the elderly, immunosuppressed hosts, pregnant females, or neonates. It can cause CNS disease, such as meningitis or cerebritis, or even sepsis.²⁷ The disease has been linked to the consumption of processed meats or unpasteurized dairy products.²⁸ There are also occasional sporadic outbreaks caused by nondairy foods, such as cantaloupe.²⁹

Another foodborne pathogen with some link to TNFI therapy is salmonellosis.³⁰ *Salmonella* is a genus of Gram-negative rods that causes gastroenteritis in normal hosts and bacteremia and osteomyelitis in compromised hosts.³¹ Foods that can be associated with salmonella infections include poultry, meats, and dairy products, such as eggs. Occasional food-specific outbreaks also occur.³²

Animal exposures

Contact with animals is a concern in patients who are initiating TNFI therapy. It is important to gather information regarding not only pets but also animals with which the patient may have experienced indirect contact (ie, rodents in the home). Some infections are transmitted between animals and humans (zoonoses), or the pathogen may reside in the animal's environment. There have been a few pathogens that have been reported with patients receiving TNFI therapy. *H capsulatum* can be found in soil contaminated with bird or bat

Table I. Example of patient-administered history flow sheet designed to elicit important information related to potential infectious complications of tumor necrosis factor–alfa inhibitor therapy

Exposure	Yes	No	Comments
Travel/residence			
Have you traveled or lived outside the United States? (Please list)			
Have you lived outside of (state or residence)? Where? When?			
Do you have future international travel plans?			
Does your home have known mold problems? Well water?			
Animals/pets			
Do you have any pets in the home, including fish?			
Have you had recent contact with farm animals? Wild animals or birds?			
Occupation			
What do you do for a living?			
Do you ever work outdoors? In the course of your work, do you disturb soil or participate in construction or demolition?			
Are you involved in health care?			
Are you a caretaker for the very young or elderly?			
Hobbies/behavioral			
Do you spend a lot of time outdoors?			
Do you garden? Wear gloves?			
Do you spend time in caves? Go spelunking?			
Do you have a lot of freshwater or saltwater exposure?			
Do you smoke cigarettes? Drink alcohol?			
Have you ever used drugs? Shared needles?			
Have you ever had a blood transfusion?			
Do you have any tattoos?			
Dietary			
Do you consume unpasteurized dairy products?			
Do you consume undercooked or raw meats or fish?			
Do you consume processed meats, including deli meats or hot dogs?			
Do you consume soft cheeses?			
Sexual			
Have you ever been tested for HIV or hepatitis?			
Have you had multiple sexual partners? Men, women, or both?			
Do you have any history of sexually transmitted infections, including herpes (oral or genital), syphilis, gonorrhea, or chlamydia?			
Have you ever had an abnormal Pap smear?			

droppings. Patients who own chickens or spend time near chicken coops, for example, could be at risk. In addition, this fungus is associated with bat droppings from other bird species.⁷ *Cryptococcus*, a ubiquitous environmental encapsulated fungus, has also been associated with the use of TNFI. *Cryptococcus neoformans* can cause CNS, pulmonary, or disseminated infections, usually in immunocompromised hosts. The fungus can be found around bird roosting sites and also has been particularly associated with pigeon droppings.³³

There appears to be an increased incidence of nontuberculous mycobacteria in the TNFI-treated patient. One species patients may encounter from pets is *M marinum*. *M marinum* is an acid-fast bacterium that typically lives in an aquatic environment. It can cause solitary or multiple skin lesions, usually on the extremities, after breaks in the

skin are exposed to ocean, salt, or fresh aquarium water. Accordingly, these lesions are commonly called “fish-tank granulomas.” Patients with nontuberculous mycobacteria who are undergoing TNFI therapy are more likely to have disseminated manifestations.³⁴⁻³⁶

There have been reports of toxoplasmosis occurring in patients who are undergoing TNFI therapy. Toxoplasmosis is caused by the protozoan *Toxoplasma gondii*.^{37,38} The primary host of this parasite is the cat family. Humans are usually infected primarily through the consumption of infected meat or hand contamination with cat feces (ie, cleaning litter boxes). Patients who become symptomatic after exposure develop a subclinical or mild influenza or mononucleosis-like illness. Afterward, healthy adults rarely experience any additional symptoms. The parasite can reactivate in

the setting of immunosuppression and disseminate to the CNS, eyes, heart, liver, or lungs.³⁹

Salmonella infections have been associated with animal exposures, including pets. A higher incidence of salmonella infection has been observed in patients with pet reptiles (eg, lizards, snakes, and turtles) or amphibians (eg, frogs).^{40,41}

Sexual history

Clinicians should obtain a comprehensive sexual history in order to identify possible sexually transmitted infections and to address risk factors. HIV and hepatitis B and C may be sexually transmitted; links between these viral pathogens and TNFI were discussed above. Human papillomavirus (HPV) infections may also be affected by TNFIs. HPV, a DNA virus responsible for infections of the skin and mucus membranes, manifests most commonly as warts, including anogenital condyloma. Certain strains are associated with malignancies of the cervix, vulva, penis, anus, and oropharynx. HPV is one of the most common sexually transmitted infections.⁴² There have been limited reports that TNFI may worsen anogenital warts, but there is no evidence at this time that they increase the incidence of the cancers associated with this virus.⁴³

Herpes simplex virus in a normal host can cause recurrent oral or genital lesions but occasionally is responsible for CNS infections. There have been a small number of reports of patients treated with TNFIs who developed herpes encephalitis.⁴⁴

Table I shows an example of a patient-administered history flow sheet that is designed to elicit important information related to potential infectious complications of TNFI therapy.

CONCLUSION

The advent of biologic therapies, including inhibitors of TNF α , represents an important advance in the management of refractory dermatologic inflammatory conditions, such as psoriasis. However, it is important to consider their mechanisms of action, their many intricate effects on immune function, and the potential for infectious consequences. Similar to patients anticipating solid or bone marrow transplantation and associated immunosuppression, it is critical to consider patients' medical and surgical histories, exposures, travel and immunization history, and to tailor necessary preventive interventions before proceeding with such therapies.

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Proactive infectious disease approach to dermatologic patients who are taking tumor necrosis factor-alfa antagonists

Part II. Screening for patients on tumor necrosis factor-alfa antagonists

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After completing this learning activity participants should be able to implement appropriate screening protocols in the pretherapeutic evaluation of psoriatic patients

considering TNF inhibitor therapy and initiate appropriate preventive and therapeutic interventions before and during such therapies, in order to best avoid infectious complications.

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Tumor necrosis factor–alfa levels are linked to disease severity in patients with inflammatory conditions, such as psoriasis. Inhibitors of this cytokine are commonly used with significant success in the treatment of such inflammatory disorders. Their use, however, can be plagued by infectious complications. An awareness of potential infections associated with these therapies is critical in order to maximize preventive efforts both before and during therapy. This review provides a guide for dermatologists caring for patients in need of this type of biologic therapy to preemptively address the infectious risks. Part II of this continuing medical education article reviews recommended screening methods for patients undergoing evaluations for tumor necrosis factor inhibitor therapy for psoriasis or other dermatologic diseases, and discusses possible prophylactic strategies to use, including the appropriate use of immunizations. (J Am Acad Dermatol 2014;71:11.e1-7.)

Key words: biologic therapy; immunizations; opportunistic infection; psoriasis; tumor necrosis factor.

SCREENING AND PROPHYLAXIS: “WHAT TO DO”

Key points

- **Tuberculosis reactivation is a well-recognized potential complication of tumor necrosis factor inhibitor therapy, and screening for latent tuberculosis should occur at baseline and yearly**
- **Certain patient populations may benefit from the use of an interferon gamma release assay instead of a purified protein derivative for tuberculosis screening**
- **Screening for endemic mycoses is controversial and should only be considered in patients with an appropriate epidemiologic exposure history**
- **A review of vaccination history before the initiation of tumor necrosis factor inhibitor therapy is a critical part of the baseline evaluation in order to determine need for additional vaccination**

Recommended screening strategies for patients receiving tumor necrosis factor inhibitor therapy are shown in Table I.

Tuberculosis

Perhaps the best-described infectious complication associated with tumor necrosis factor inhibitors (TNFIs) is tuberculosis (TB). Beginning in 2002, recommendations for screening and potential treatment of latent TB infection were implemented. Adherence to these guidelines later caused a significant decrease in the rates of TB in a population of infliximab-treated patients.¹ The Centers for Disease

Control and Prevention (CDC) recommend TB testing before starting treatment with TNFIs.² Most of the initial recommendations involve using a tuberculin skin test (TST) for the diagnosis of latent TB infection (LTBI). Using a boosted TST (2-stage TST) has led to increased LTBI detection in these patients.¹ Over the last few years, interferon gamma release assays (IGRAs) have been increasingly used to diagnose LTBI, and available data suggest that their performance is not inferior to TSTs. The benefits to using this test as a screening tool include ease of testing (ie, no follow-up visit required, less subjectivity in interpreting results) and increased specificity in patients previously given Bacillus-Calmette-Guérin (BCG) vaccine.³ There are limited data in patients receiving TNFIs, and the test's ability to detect LTBI compared to TSTs has yet to be comprehensively evaluated in this population. One small retrospective study in the psoriasis population, however, advocates for using IGRA over TST given its stronger association with LTBI diagnosis, but it is important to note that 90% of the patients in the study had a previous BCG vaccination⁴—a population in which IGRAs are known to be more specific. Certain patients undergoing evaluation for TNFI therapy may warrant the use of an IGRA over a TST, such as those who have a history of BCG vaccination or those who are less likely to return for repeat examination.

Histoplasmosis

In terms of the existing data regarding endemic mycoses, histoplasmosis is the best studied in the setting of TNFI therapy. Initially, there was some speculation regarding potential screening for this infection before the initiation of biologic therapy

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Table I. Recommended screening strategies for patients receiving tumor necrosis factor inhibitor therapy

Disease entity	Screening test	Timing
Tuberculosis	PPD or serum IGRA	Baseline and annually
HIV	Serology (ELISA) and confirmatory Western blot	Baseline*
Hepatitis B	Hepatitis B surface antigen, surface antibody, and core total antibody (HBV DNA quantitative level if surface antigen or core antibody positive)	Baseline*
Hepatitis C	Serology (EIA) and HCV RNA quantitative level if serology positive	Baseline*
Histoplasmosis	Serology and chest radiography	Consider at baseline ONLY IF appropriate epidemiologic history
Coccidioidomycosis	Serology and chest radiography	Consider at baseline, ONLY IF appropriate epidemiologic history
HPV	Cervical Papanicolaou testing/HPV DNA testing	Baseline and annually
Strongyloidiasis	Serology	Baseline if appropriate epidemiologic history

EIA, Enzyme immunoassay; ELISA, enzyme-linked immunosorbent assay; HPV, human papillomavirus; IGRA, interferon gamma release assay; PPD, purified protein derivative; RNA, ribonucleic acid.

*Patients who have ongoing increased risk because of behavior, exposure, etc may warrant serial screening.

using serology or antigen testing. At this point, in an asymptomatic patient, there appears to be no role in actively screening patients given the lack of clear-cut benefits in predicting infection. If a patient, however, engages in high-risk activities in endemic areas, such as those mentioned previously, or has had recent symptoms consistent with histoplasmosis, then a chest radiograph to look for active disease should be performed before the initiation of therapy. Antifungal prophylaxis is not currently recommended for asymptomatic patients living in endemic area because of the uncertainty of the actual risk of reactivation.⁵

Coccidioidomycosis

There is a paucity of data regarding screening for *Coccidioides immitis* before TNFI therapy. In an endemic area, coccidioidal serologic tests could be considered before starting TNFI therapy to establish a baseline; a chest radiograph to look for evidence of active disease could also be performed. Like histoplasmosis, many cases are acute rather than a reactivation, so these tests may not be clinically useful.⁶

Hepatitis B

Management with TNFI therapy can be challenging in the hepatitis B-positive patient. Previous guidelines have addressed hepatitis B as being a relative contraindication to these medications. A recent review in the dermatology literature summarizes key aspects of hepatitis B infection, including differences in serologic status and risk of infection.^{7,8} Many experts recommend beginning therapy for confirmed chronic hepatitis B infection (positive surface antigen and HBV DNA) with a

nucleos(t)ide inhibitor before initiating TNFI therapy in order to avoid potential exacerbations. Uncertainty exists when patients have negative surface antigen and antibody results but have positive core antibody with or without detectable DNA, suggesting exposure to the virus in the past. Although the large majority of these patients have cleared the virus, the lack of surface antibody suggests a lack of protective immunity, thereby raising concern for reactivation on immunosuppressive drugs. While the risk of reactivation in these patients is likely quite low (approximately 10% according to some authors), many experts recommend considering prophylactic treatment with antivirals in these patients.^{7,8}

Hepatitis C

As mentioned above, acute exacerbation of hepatitis C is less common in patients treated with TNFI therapy than in patients with hepatitis B.⁹⁻¹¹ There are limited data, however, addressing the relative long-term risks of these agents and their contribution to the development of chronic liver disease, including cirrhosis and fibrosis. Treatment, however, does appear to be less complicated than in hepatitis B. Patients with active hepatitis C disease should be treated appropriately with standard therapy regardless of the need for TNFI therapy. Close monitoring and follow-up with an expert is recommended, especially in patients with more advanced stages of liver disease.⁷

HIV

The role of TNFI therapy in HIV is controversial. Like hepatitis C, it appears that the experience in

treating HIV patients has been relatively safe, although limited conclusive evidence is available.¹² However, administering an immunosuppressive medication to an already immunosuppressed individual is disconcerting. There was some suggestion that starting highly active antiretroviral therapy (HAART) earlier would be prudent in patients concomitantly on TNFI therapy; however, this point has become moot, with recent guidelines suggesting that most HIV patients be started on HAART regardless of CD4 counts.¹³ Another interesting but unclear topic is whether to use prophylaxis at higher CD4 counts against pathogens, like *Pneumocystis jirovecii*, that are common in AIDS and are associated with TNFI therapy.

It appears that TNFI therapy may be considered if indicated in patients who are controlled on HAART with satisfactory CD4 counts and who have no evidence of ongoing opportunistic infections. These patients should have close follow-up with an HIV specialist.⁷

Strongyloides

There have been multiple reports of strongyloides infections in patients taking a variety of different immunosuppressive medications. In patients from endemic areas, screening for latent infections may be beneficial to prevent active disease before the initiation of TNFI therapy. Serologic testing is probably the most widely available and sensitive method of diagnosing chronic asymptomatic infections, and chemoprophylaxis with an agent such as ivermectin may prevent disseminated disease.¹⁴

IMMUNIZATIONS: “WHAT I NEED TO KNOW”

The prevention of illness through appropriate vaccinations before TNFI therapy is an important consideration for the practitioner. Patients planning to undergo TNFI therapy may be at an increased risk of vaccine-preventable illnesses. The immunosuppressive nature of therapy may reduce the response to vaccination once TNFI therapy is initiated. A thorough vaccination history should be elicited to identify gaps in pediatric vaccine coverage, current vaccination needs, and the potential need for future vaccinations. Generally, the administration of live attenuated vaccines is contraindicated in immunocompromised individuals. Patients who have already begun or who have recently stopped TNFI should be considered immunocompromised. In general, the half-life of the biologic agent should guide timing of vaccination, with a minimum of 4 to 5 half-lives as a conservative estimate.^{15,16} Therefore,

patients who are anticipating the initiation of TNFI therapy in the near future should receive any indicated vaccinations before therapy whenever possible. In some cases, the clinician may wish to consider vaccination outside of standard guidelines for patients who are likely to meet accepted indications during the period of anticipated immunosuppression.

Live vaccinations are a particular concern for the TNFI-treated patient. The live vaccines that are usually recommended in patients include measles, mumps, rubella (MMR), varicella vaccine, and herpes zoster vaccine. Special circumstances, such as anticipated international travel, may lead to vaccination with other live vaccines, such as yellow fever or typhoid, under normal circumstances, and should be addressed before beginning TNFI therapy whenever possible.

Any adult with an unknown vaccination status to MMR should have serologic titers assessed, and if immunity is documented, further vaccination is not warranted. If no documented immunity exists, then the patient should be vaccinated, usually with trivalent MMR vaccine, although univalent vaccine for the individual components may be available in some settings. Given the risk of prolonged viremia in any patient, a waiting time of at least 6 weeks should take place between the time of vaccination and the start of immunosuppressive therapy.

The varicella vaccine is administered to persons without a history of varicella infection. Titers can be drawn for all those without a known history, and if positive do not warrant vaccination. There are limited data for an acceptable interval between vaccination and the onset of immunosuppressive therapy. Extrapolated from information regarding the herpes zoster vaccine, which contains a significantly larger amount of varicella zoster virus, an interval of at least 4 weeks is recommended before the initiation of TNFI therapy.^{15,16}

To prevent the reactivation of varicella zoster virus, the herpes zoster vaccine is routinely recommended for individuals ≥ 60 years of age. The CDC recommends this age as a cutoff, but the US Food and Drug Administration approved a lowered age limit of 50 in 2011.¹⁷ Although the vaccine is more effective for this age range, the risk of herpes zoster is also lower.¹⁸ If a patient is to undergo future immunosuppression, administration of the vaccine to patients in this younger age range should be considered. Data are limited, but waiting 4 weeks to 3 months between vaccination and commencement of immunosuppressive therapy has been proposed to avoid the risk of dissemination.^{15,19}

Killed or inactivated vaccines are generally safe in immunosuppressed individuals. These vaccinations, however, should be administered before immunosuppression whenever possible to minimize the blunting of subsequent immune responses. Vaccination with inactivated vaccines generally follows the current guidelines for the nonimmunosuppressed adult.

Patients should receive the tetanus and diphtheria vaccine every 10 years, with the tetanus, diphtheria, and acellular pertussis vaccine administered 1 time during the time period before therapy initiation.

The inactivated influenza vaccine should be given yearly at the beginning of the influenza season. The live, intranasal form should be avoided while treating with biologic agents.¹⁵

The recent recommendation by the Advisory Committee on Immunization Practices (ACIP) is that adults with immunocompromised conditions who are ≥ 19 years of age receive the 13-valent pneumococcal conjugate vaccine (PCV13), followed by the PPSV23 vaccine, which is routinely recommended for adults 19 to 64 years of age who are receiving immunosuppressive therapy.²⁰ Vaccination in the setting of anticipated immunosuppression in the near term may be prudent to assure a maximal vaccine response.

As mentioned above, hepatitis B serologies should be checked, and if a patient has been unexposed a vaccination series should be instituted. Hepatitis A vaccination should also be offered alone or in combination with hepatitis B vaccination to previously unvaccinated or unexposed individuals.

Meningococcal vaccination should be given to at-risk individuals (ie, college students and military recruits) that have previously not received it.¹⁵

There are currently 2 types of HPV vaccines available. The quadrivalent human papillomavirus vaccine (Gardasil, Merck and Co, Whitehouse Station, NJ) can routinely be given in males and females at 11 to 12 years of age and considered as early as 9 years of age. Catch-up vaccination is also recommended for 13- through 26-year-old females and 13- through 21-year-old males who have not completed the series. Vaccination in males is routinely recommended for men 22 to 26 years of age who either have sex with men or who are immunocompromised.²¹⁻²³

The most recent iteration of the ACIP Recommended Immunization Schedule for Adults Aged 19 Years and Older is summarized in Table II.²⁴ Specific recommendations pertaining to immunocompromised patients are relevant to those who have already begun TNFI therapy. As stated above,

the administration of live vaccines is contraindicated in these patients, and any live vaccine should be administered a minimum of 6 to 12 weeks before initiating therapy.¹⁵ Inactivated vaccines may be administered once therapy has begun, but all vaccines require time after administration to induce an adequate immune response. Data on the exact timing of inactivated vaccine administration are anecdotal at best, but a reasonable approach would be to vaccinate as early as possible before beginning TNFI therapy, ideally 2 to 4 weeks earlier.

ADDITIONAL COUNSELING: “WHAT TO SAY”

Given that the majority of reports of infections associated with TNFI therapy comes from case reports and small series, it is difficult to stratify infectious risk when counseling about avoiding future exposures.

Patients should be made aware of possible areas where they may be more susceptible to an endemic infection. If travel to these areas cannot be avoided, then patients should stay away from activities that may put them at higher risk for acquiring these infections. It is important that individuals who have to travel internationally be evaluated by a travel specialist—especially when traveling to underdeveloped nations. Required live vaccines, such as yellow fever vaccine, should be considered and administered well before the initiation of TNFI therapy. Vaccination for *Salmonella typhi* may be inactivated or live-attenuated. The live-attenuated vaccine, which is longer-acting, should only be given well in advance of TNFI therapy; the patient who is already undergoing TNFI therapy should be given the inactivated typhoid vaccine for anticipated potential exposure.

Patients should restrict their participation in recreational or occupational activities that may place them at risk of acquiring an environmental infectious agent (ie, Nocardia species, atypical mycobacteria, and Aspergillus species). If patients have occupations that place them at risk (ie, housing demolition) then the proper precautions should be taken, such as wearing a respirator.

Patients should avoid living in buildings contaminated with mold spores. They should make sure to minimize contact with decomposing plant matter or soil that may harbor fungi in their homes.

Undercooked meats or unpasteurized dairy products may transmit *Listeria monocytogenes*. Classic associations, such as processed meats, including previously cooked or cured deli meats or hot dogs, should be avoided or reheated thoroughly before ingestion. Soft cheeses and meat pates should be avoided.

Table II. Advisory Committee on Immunization Practices recommended immunization schedule for patients >19 years of age, including immunocompromised patients (2013)²⁴

Vaccine	Dosing schedule	Notes for immunocompromised patients*
Influenza	1 dose annually	Inactivated vaccine ONLY
Td/Tdap	Substitute 1-time Tdap for booster; then boost with Td every 10 years	Same
Human papillomavirus	3 doses through age 26	Same
PPSV23	1 or 2 doses	1 or 2 doses
PCV13	1 dose	1 dose (if PPSV23 naïve, patients should receive a single dose of PCV 13 followed by a dose of PPSV at least 8 weeks later; patients who previously received PPSV23 should receive a dose of PCV13 ≥ 1 years after the last PPSV23 dose)
Meningococcal	1 or 2 doses [†]	1 or 2 doses [†]
Hepatitis A	2 doses if titer negative	2 doses if titer negative
Hepatitis B	3 doses if titer negative; check postvaccine titer 1 month after series completion; if negative revaccinate	3 doses if titer negative; check postvaccine titer 1 month after series completion; if negative revaccinate; consider use of 40 μ g/mL dose
Varicella	2 doses in adults if titer negative and/or no history of varicella infection	Contraindicated
Zoster	1 dose in adults ≥ 60 of age	Contraindicated
MMR	1 or 2 doses if titer negative	Contraindicated

MMR, Measles, mumps, rubella; PCV13, pneumococcal 13-valent conjugate; PPSV23, pneumococcal polysaccharide; Td, tetanus/diphtheria; Tdap, tetanus, diphtheria, and pertussis.

*Patients already receiving tumor necrosis factor inhibitor therapy are considered "immunocompromised."

[†]Patients with functional asplenia or complement component deficiencies should receive 2 doses of conjugate vaccine quadrivalent at least 2 months apart. See full Advisory Committee on Immunization Practices recommendations²⁴ for other at-risk populations.

Patients should exercise caution with any animal exposures. Although most standard household pets do not represent an overwhelming risk to patients, some extra care may be able to prevent infections. Avoiding the inhalation of soil contaminated with stool or droppings of bird species such as pigeons or chickens is important. Hand washing after animal contact, even pets, should be stressed; this is especially true for amphibians and reptiles. Animal scratches and bites should be cleansed thoroughly and reported to a health care professional. If a person has never been around cats or is known to be serologically negative to toxoplasmosis, care should be taken to avoid exposure while undergoing TNFI therapy and to avoid activities such as cleaning litter boxes. Patients with aquarium fish can minimize risk of *Mycobacterium marinum* infections by not cleaning tanks or by wearing gloves with any fish or aquarium water contact.

In addition, patients should be encouraged to always practice safe sex. Condoms are the most effective barrier to transmitting infectious diseases via coitus, although the transmission of certain pathogens like HPV can still be transmitted despite their use. Papanicolaou smears must be routinely performed in females.

Patients with active, acute infections should not be started on TNFI therapy. If an infection develops while undergoing TNFI therapy, these medications should be held until there is resolution. In addition, patients should not hesitate to report any medical illness, because they may develop infections that are quicker in onset and progression than in the normal host. In certain unusual circumstances (eg, long geographic distance or delay to an appropriate location for urgent evaluation), the clinician may consider providing antibiotics for self-administration to avoid delays in initiating therapy for serious bacterial sepsis. Frequent hand washing, especially after contact with sick individuals or potential environmental sources, should be encouraged.

A full history and comprehensive physical examination should be performed at least yearly in patients receiving TNFI therapy. Any new or unusual complaints or physical findings should prompt careful consideration and investigation, given the myriad possibilities of potential infectious complications, from typical bacterial infections to unusual parasitic infestations. Additional workup should be guided by specific findings, and may require assistance from an infectious diseases specialist.

CONCLUSION

The advent of biologic therapies, including inhibitors of tumor necrosis factor-alfa, represents an important advance in the management of several refractory dermatologic inflammatory conditions. Because of the anticipated drug-induced altered immunity, appropriate screening (via obtaining a patient's medical history, surgical history, previous immunizations, and travel history) and prophylactic treatment when appropriate are advised. The clinician should counsel patients how to minimize their exposure to potential pathogens, and encourage rapid reevaluation for any question of new infectious complications of TNFI therapy. These recommendations serve as guidelines for dermatologists, in consultation with infectious disease specialists, to help manage their patients who would benefit from TNFI therapy.

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Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer

Part I. Conventional chemotherapeutic drugs

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Conventional chemotherapy continues to be an important part of cancer management, but may cause various cutaneous reactions because it disturbs specific cell cycle phases. The alkylating agents cyclophosphamide, ifosfamide, and thiotepa can produce hyperpigmentation, while hypersensitivity reactions can be seen with platinum alkylating agents. Antimetabolites vary in reactions from exanthematous to bullous skin lesions. 5-fluorouracil and its derivatives and liposomal doxorubicin and daunorubicin are characteristically known to cause hand-foot syndrome, while bleomycin can cause fibrosis and flagellate dermatitis. Several hypersensitivity reactions may also occur from mitotic inhibitors and topoisomerase inhibitors. These different characteristic presentations are important to dermatologists in identifying the correct diagnosis and management for the cancer patient. (J Am Acad Dermatol 2014;71:203.e1-12.)

Key words: cancer; chemotherapy; cutaneous reactions; cytotoxic therapy; drug hypersensitivity; rash.

Cancer therapy has always been a challenging focus in clinical medicine and research. Traditionally, chemotherapeutic drugs have worked by disrupting specific phases of the cell cycle in actively dividing cancer cells (Table I).¹ In doing so, it can cause multiple side effects, with the skin being one of the most commonly affected organs, manifesting as dermatitis, alopecia, stomatitis, and other adverse reactions. Characteristics of these cutaneous reactions vary depending on the chemotherapeutic drug. Identification of these reactions is important to both dermatologists and oncologists so that appropriate management and uninterrupted chemotherapy may be provided to cancer patients.

ALKYLATING AGENTS

Key points

- Self-limiting hyperpigmentation may occur with alkylating agents, especially in occluded areas with the use of ifosfamide and thiotepa
- Type I immunoglobulin E-mediated hypersensitivity reactions can occur with platinum agents

Cyclophosphamide, ifosfamide, and thiotepa

Classical alkylating agents attach an alkyl group to the guanine base of DNA, and are used to treat leukemia, lymphoma, Hodgkin disease, multiple myeloma, sarcoma, and cancers of the lung, breast, and ovary.¹ All can be administered intravenously, though cyclophosphamide also has an oral option, and thiotepa an intracavitory protocol.

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Abbreviations used:

5-FU:	5-fluorouracil
CLL:	chronic lymphocytic leukemia
HFS:	hand–foot syndrome
NHL:	non-Hodgkin lymphoma
NSCLC:	non–small cell lung carcinoma

Hyperpigmentation. Cyclophosphamide can cause hyperpigmented patches after 4 weeks of therapy that fade within 6 to 12 months after discontinuation. These patches can appear on the palms, soles, nails, teeth and, rarely, the gingiva. Nails can have diffuse, longitudinal, or transverse pigmentation, and may also present with onychodystrophy, onycholysis, Beau lines, or Muehrke lines.^{2,3} Hyperpigmentation from ifosfamide often occurs in the flexural areas, on the hands, feet, and scrotum, and under occlusive dressings. Large areas of the trunk may also be affected in severe cases. This discoloration can occur after a single course or many months of therapy, and has a more unpredictable course than that from cyclophosphamide. Some cases may experience fading despite continued treatment, whereas others may persist even after completing treatment.^{2,4,5}

Like ifosfamide, thiotepa can produce hyperpigmentation under occluded areas. Other commonly reported cutaneous side effects include erythema, desquamation, and pruritus.⁶ Horn et al⁷ found that thiotepa is excreted in sweat, and it has been postulated that this mechanism is responsible for the drug's toxicity.

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Table I. Mechanism of action and cutaneous reactions of conventional chemotherapeutic drugs

Drug class	Mechanism of action	Cutaneous reactions
Alkylating agents	Crosslink with DNA molecules and damage cells in all phases of the cell cycle	
Classical alkylating Cyclophosphamide, ifosfamide, and thiotepa		Hyperpigmentation, alopecia, urticarial hypersensitivity, neutrophilic eccrine hidradenitis, porphyria cutanea tarda, and radiation recall
Platinum agents Cisplatin, carboplatin, and oxaliplatin		Hypersensitivity, hyperpigmentation, alopecia, and radiation recall
Antimetabolites	Substitute building blocks of DNA and RNA and damage cells in the S phase	
Analogs Fludarabine, cladribine, gemcitabine, and pemetrexed		Maculopapular or bullous reactions
Fluorouracil 5-fluorouracil, capecitabine, and tegafur		HFS, photosensitivity, hyperpigmentation, alopecia, stomatitis, inflammation of actinic keratosis, cutaneous lupus, pyogenic granuloma, and granulomatous septal panniculitis
Antitumor antibiotics		
Anthracyclines Doxorubicin and daunorubicin	Intercalate with DNA base pairs and interfere with topoisomerase II in all cell cycle phases	HFS, follicular rash, intertrigo-like eruption melanotic macules, and radiation recall ⁶⁸
Bleomycin	Induce DNA strand breaks at G2 phase	Flagellate dermatoses, pigmentation, fibrosis, Raynaud phenomenon, and nail changes
Mitotic inhibitors	Prevent the formation of spindles or microtubules during the M phase	
Taxanes Docetaxel and paclitaxel		Taxane-induced HFS, nail changes, alopecia hypersensitivity, and edema
Vinca alkaloids Vincristine, vinblastine, and vinorelbine		Alopecia, maculopapular rash, erythema multiforme-like lesions, and HFS
Topoisomerase inhibitors	Interfere with topoisomerase I or II during DNA replication in all cells in the S or G2 phase	
Topoisomerase I Topotecan and irinotecan		Gastrointestinal disturbance, myelosuppression, hair loss, and hypersensitivity
Topoisomerase II Etoposide, teniposide, and amsacrine		HFS, paronychia, hair loss, perianal irritation, myelosuppression, gastrointestinal distress, and allergic reaction

HFS, Hand–foot syndrome.

Other reactions. Patients receiving alkylating agents can experience pain and phlebitis at the infusion site, and with time, can develop sclerosis and hyperpigmentation along the vein. Urticarial hypersensitivity reactions may also occur on administration.² Anagen effluvium from these agents presents within 7 to 10 days of initiation, and regrowth of hair can be expected once the agents are discontinued.^{2,8} Other less common cutaneous reactions reported that are usually caused by cyclophosphamide include neutrophilic eccrine hidradenitis,⁹ porphyria cutanea tarda,¹⁰ and radiation recall.¹¹

Cisplatin, carboplatin, and oxaliplatin

Platinum agents form reactive platinum complexes that crosslink with DNA molecules, inhibiting DNA synthesis and repair, and are given intravenously. Cisplatin is an older drug that causes many side effects (eg, ototoxicity, neurotoxicity, nephrotoxicity, and emetogenicity) and is used to treat a wide variety of solid tumors. Carboplatin and oxaliplatin are newer generation platinum agents with less toxicity.¹²

Hypersensitivity. Type I immunoglobulin E-mediated hypersensitivity reactions can occur with platinum agents and typically develop after multiple treatments. Palmar pruritus, flushing, urticaria, anaphylaxis, and abdominal cramping may occur within minutes to hours of infusion. Cisplatin reactions appear most frequently between the fourth and eighth courses, whereas reactions to carboplatin and oxaliplatin mostly occur after the sixth course.¹³ Intradermal skin testing is positive in >80% of reactive patients, and 1 study has recommended it to predict hypersensitivity in patients who are scheduled to undergo the readministration of platinum salts—especially before the eighth dose.^{13,14} However, skin test screening for all patients remains controversial, and larger studies are needed to establish proper guidelines.¹³ Allergic patients can be managed with a slower infusion rate and premedication with antihistamines and corticosteroids. Desensitization can also be performed.

Other reactions. Platinum agents may cause extravasation injury during administration. In addition, cisplatin produces hyperpigmentation in 70% of patients, which can be localized or patchy, and can affect the hair, nails, and oral mucosa. This risk increases with subsequent courses.^{2,15} Anagen effluvium and permanent alopecia from cisplatin and carboplatin have also been reported,^{16,17} while radiation recall has been reported in association with oxaliplatin.

ANTIMETABOLITES

Key points

- Maculopapular or bullous reactions may occur from fludarabine, cladribine, gemcitabine, and pemetrexed
- Hand–foot syndrome can result from 5-fluorouracil, capecitabine, and tegafur, as well as photosensitivity and hyperpigmentation of the skin, mucosa, and nails

Fludarabine, cladribine, gemcitabine, and pemetrexed

Fludarabine is an intravenous or oral purine analog that interferes with nucleotide synthesis that is used for the palliative treatment of patients with chronic lymphocytic leukemia (CLL), non-Hodgkin lymphoma (NHL), Waldenström macroglobulinemia, and other low grade lymphoid malignancies. Autoimmune reactions, such as hemolytic anemia and thrombocytopenia, have been reported to occur with its use.¹⁸ Paraneoplastic pemphigus (PNP), an autoimmune blistering disorder characterized by painful skin bullae and mucosal erosions, has been reported to occur with fludarabine and several cases of NHL and CLL.^{19,20} The bullous lesions of PNP appeared after 1 to 9 pulses of fludarabine and after 2 to 14 days from its administration. Lesions improved after the administration of immunosuppressive drugs and the withdrawal of fludarabine. Hypothesized possible mechanisms are the induction of particular autoantibodies to the skin by fludarabine or the induction of drug-induced antitumor antibodies that cross react with epidermal proteins. Other cutaneous reactions to fludarabine are maculopapular rash, stomatitis, and acral erythema.¹²

Cladribine is also a purine analog used for the intravenous treatment of hairy cell leukemia, CLL, cutaneous T-cell lymphoma, NHL, and Waldenström macroglobulinemia. In 1 study, cutaneous reactions were reported to occur in 21% of patients²¹ and are thought to be related to T cell imbalances induced by the drug. Maculopapular rashes have been described in patients with hairy cell leukemia treated by cladribine,²² with 1 case of toxic epidermal necrosis,²¹ and 2 cases of a generalized purpuric rash.²³ An eosinophilic dermatitis with histologic features of Wells syndrome has been seen in several advanced CLL cases.²⁴ A generalized rash in CLL patients after 1 to 2 courses of cladribine featured an eosinophil-rich infiltrate with flame figures similar to Wells syndrome (eosinophilic cellulitis), and corticosteroids were effective to control the eruptions.

Gemcitabine is an intravenous deoxycytidine analog with antineoplastic activity against solid

tumors, such as non–small cell lung carcinoma (NSCLC), ovarian, breast, pancreatic, and head and neck cancer.¹² Skin reactions occur in 25% to 39% of patients, including alopecia and maculopapular rash.²⁵ Bullous reactions have been described in 1 case with linear immunoglobulin A deposition and another case without immunoglobulin deposition.^{26,27} Stevens–Johnson syndrome/toxic epidermal necrolysis overlap in a patient undergoing radiotherapy with gemcitabine has also been reported.²⁸ In patients with lower extremity lymphedema, erysipeloid rash, pseudocellulitis, and pseudosclerodermatous reactions have been observed.^{29–31} It is suspected that in areas with impaired lymphatic drainage, gemcitabine pharmacokinetics may be altered, with slower inactivation and accumulation of the drug in the subcutaneous tissue and skin. Gemcitabine has also been reported in 13 cases to cause radiation recall in both cutaneous (30%) and internal organ tissues (70%).³²

Pemetrexed is an intravenously administered folate analog that interferes with enzymes required for pyrimidine and purine synthesis, and is used for the treatment of mesothelioma, NSCLC, and breast, head, and neck carcinoma. It is known to cause hematologic and cutaneous toxicities; premedication with vitamin B₁₂, folate, and dexamethasone is generally advised. A pruritic generalized rash occurs in most patients, with 1 phase II study finding it in 79% of 33 patients.³³ Another prospective cohort study reported cutaneous reactions in 35% of its 107 patients, with conjunctivitis as the most common adverse reaction, followed by periorbital and leg edema.³⁴ Other uncommon reported reactions to pemetrexed include asteatotic eczema,³⁵ hyperpigmentation of the palms and soles,³⁶ urticarial vasculitis,³⁷ melanonychia and onycholysis,³⁸ toxic epidermal necrolysis,³⁹ acute generalized exanthematous pustulosis,⁴⁰ and radiation recall dermatitis.⁴¹

5-Fluorouracil, capecitabine, and tegafur

5-Fluorouracil (5-FU) is a pyrimidine analog that inhibits the enzyme thymidylate synthase, thereby interrupting thymidine synthesis required for DNA replication, and can cause myelosuppression, diarrhea, mucositis, and dermatitis. Capecitabine and tegafur are orally administered prodrugs especially used for colon and gastrointestinal neoplasms. They are designed to be well absorbed from the gastrointestinal tract and converted to 5-FU in the liver or within the tumor at lower concentrations than 5-FU intravenous dosages, thereby minimizing toxicity.⁴²

Hand–foot syndrome. Hand–foot syndrome (HFS), or palmoplantar erythrodysesthesia, is

characterized by a prodrome of pain and tingling at the extremities followed by a symmetric, sharply demarcated erythema of the palms and soles within the first 2 cycles of therapy. Vesicles and bullae may eventually appear, desquamate, and later involve the dorsal surfaces of the hands and feet. Improvement is noted once the treatment dose is decreased or discontinued, and recurrence in the next treatment cycle is the norm. HFS has been reported in a wide range of chemotherapy drugs, with the most common agents being 5-FU, capecitabine, pegylated liposomal doxorubicin, and cytarabine⁴³ (Fig 1).

The histologic findings of HFS are nonspecific, and its pathophysiology is not fully understood.⁴³ HFS grading and management include: grade 1 (ie, mild erythema and slight or no dysesthesia) managed with supportive care, topical steroids, and urea; grade 2 (ie, skin redness, dysesthesias, and pain) managed with topical steroids, keratolytics, and nonsteroidal antiinflammatory drugs; and grade 3 (ie, severe blistering, desquamation, pain, and impaired function) managed with drug discontinuation.⁴⁴ Premedication with pyridoxine and/or oral dexamethasone are advised in some patients, but the data are insufficient to recommend their routine use.^{45–47}

5-FU has a low incidence of acral erythema when administered as a bolus, but can occur more frequently when given as a prolonged infusion.⁴⁸ Capecitabine has a higher incidence (53%) than 5-FU (6%) because, as an oral agent, it mimics prolonged infusion.⁴⁹ Tegafur, on the other hand, has a lower incidence (2%).⁵⁰ Subsequent acral hyperpigmentation^{51,52} and palmoplantar keratoderma^{53,54} may result from chronic HFS induced by capecitabine and tegafur. Subsequent acral necrosis and scleroderma-like changes may also occur with the use of capecitabine.^{55,56}

Hyperpigmentation. Pigmentation from 5-FU can have a varied appearance, including the following: (1) photodistributed, (2) serpentine supravenous hyperpigmentation from hand to shoulder, (3) widespread reticulate hyperpigmentation, (4) serpentine streaks in the back and buttocks, and (5) acral pigmentation.² The discoloration can occur immediately after sun exposure or as a delayed reaction after several days of therapy. Pigmentation may fade gradually over time, and may not recur in subsequent infusions. Capecitabine and tegafur, on the other hand, cause mainly acral pigmentation in several case reports. Hyperpigmentation may be diffuse, along the crease lines, or macular over the palms and soles.^{52,53,57} Mucosal macular pigmentation from capecitabine has been reported



Fig 1. Hand–foot syndrome from antimetabolites and anthracyclines. (**A**) Well demarcated erythema on the feet, (**B**) palms, (**C**) soles, and (**D**) associated nail changes. (Photo courtesy of Mario E. Lacouture, MD, Memorial Sloan Kettering, New York, NY.)

on the tongue and from tegafur on the glans penis and lip.^{53,55}

Nails. 5-FU may cause diffuse melanonychia, transverse bands, or half and half–like nails, and there have been reports of onycholysis, paronychia, and thickening of the nail with its use.² Capecitabine and tegafur also cause longitudinal melanonychia^{2,58}; however, onycholysis and onychomadesis has only been seen with capecitabine.⁵⁹

Photosensitivity. Ultraviolet light may produce phototoxicity, hyperpigmentation, or an erythematous rash on exposed skin with the use of 5-FU.² Photosensitivity reported in relation to tegafur, on the other hand, may be lichenoid or eczematous in presentation.⁶⁰ Two cases of an eczematous photosensitive reaction have been described with capecitabine.^{61,62}

Other reactions. Alopecia and stomatitis occur in 5-FU patients (21% and 62%, respectively) and less commonly in patients who are taking capecitabine (6% and 24%, respectively).⁴¹ Inflammation of actinic keratosis (Fig 2) and radiation recall have also been well documented from use of 5-FU and capecitabine. This may be because actinic keratosis and irradiated cells both



Fig 2. Actinic keratoses in a patient taking 5-fluorouracil. (Photograph courtesy of Richard Johnson, MD.)

have transformed keratinocytes with damaged DNA that is prone to additional 5-FU–induced cell injury, leading to inflammation.^{2,63,64} Several cases of subacute and discoid cutaneous lupus have also been reported.^{65,66} A possible hypothesis is that 5-FU agents affect epidermal keratinocytes and trigger the development of lupus erythematosus–like eruptions in individuals with anti-SSA/Ro antibodies. Other capecitabine-induced reactions described in single case reports include pyogenic granuloma^{67,68} and granulomatous septal panniculitis.⁶⁹

ANTITUMOR ANTIBIOTICS

Key points

- Hand–foot syndrome may result from liposomal anthracyclines
- Flagellate dermatoses, pigmentation, and fibrosis may result from bleomycin, with Raynaud phenomenon and nail changes reported after intralesional administration

Doxorubicin and daunorubicin

The anthracyclines doxorubicin and daunorubicin are derived from the bacterium *Streptomyces peucetius* var. *caesius* and are used to treat various hematologic malignancies and solid tumors. The main adverse effect is cardiotoxicity, which is limited in the liposomal pegylated or encapsulated form of anthracyclines used for non-Hodgkin lymphoma, multiple myeloma, NSCLC, AIDS-related Kaposi sarcoma, and refractory ovarian cancer.⁷⁰ Both drugs are administered intravenously.

HFS. HFS from anthracyclines presents similarly as HFS caused by antimetabolites (see above). HFS occurs in 29% to 49% of doxorubicin patients, and less commonly with daunorubicin.⁴⁶ Its onset is within the first 2 to 3 cycles of treatment, and it is usually self-limiting, with resolution reported within 1 to 5 weeks of medication discontinuation.⁴⁷

Other reactions. Alopecia occurred in 7% of patients, and mucositis was reported in 37% of patients in a community-based observation study on liposomal doxorubicin.⁷¹ Other uncommon skin reactions that have been seen include diffuse follicular rash, intertrigo-like eruption in the axilla, groin, and waist, melanotic macules on the trunk and extremities, and radiation recall.⁷²

Bleomycin

Bleomycin is a glycopeptide produced by the bacterium *Streptomyces verticillus*, and it is used for the treatment of squamous cell carcinoma, lymphoma, testicular carcinoma, and malignant pleural effusion. It can be administered intravenously, intramuscularly, intraperitoneally, intrapleurally, or given as an intralesional injection in recalcitrant warts, keloids, and scars.⁷³ Toxicity to bleomycin occurs in the lungs and skin because these organs lack bleomycin hydrolase, an inactivating enzyme.⁷⁴ Pulmonary fibrosis is a serious complication of high doses (ie, >400 units), while cutaneous reactions usually occur between 200 to 300 units.⁷³

Flagellate dermatitis and pigmentation. Whiplike erythematous reactions over the trunk or extremities occur in 20% to 30% of patients who are taking bleomycin, and can appear 12 to 24 hours up to 6 months after drug induction.⁷⁴ They appear as

pruritic erythematous linear streaks with or without reaction to trauma or scratching, and heal with hyperpigmentation. The lesions are self-limiting with the cessation of the drug and recur upon reexposure; recurrence is often more severe and widespread.

Fibrosis. Scleroderma has been reported after bleomycin treatment with cumulative doses between 51 and 780 units. Affected patients had no evidence of internal involvement, and lesions resolved either spontaneously or with steroid use and bleomycin discontinuation.⁷³ Raynaud phenomenon can occur, especially after intralesional injection into recalcitrant warts, and may be related to drug-induced vascular endothelial injury. Fingertip necrosis caused by bleomycin has been reported after several months of Raynaud phenomenon.⁷⁵

Other reactions. Bleomycin may cause alopecia, nail dystrophy, and horizontal or vertical nail pigmentation.⁷³

MITOTIC/SPINDLE INHIBITORS

Key points

- Taxanes may cause hand–foot syndrome, nail changes, hypersensitivity, peripheral neuropathy, neutropenia, edema, and alopecia
- Vinca alkaloids may cause peripheral neuropathy, rash, and hand–foot syndrome

Paclitaxel and docetaxel

The taxanes are a group of drugs that were initially derived from yew trees, and function by interfering with microtubules. Paclitaxel was the first taxane discovered, and is currently approved by the US Food and Drug Administration for the treatment of breast cancer, NSCLC, AIDS-related Kaposi sarcoma, and ovarian cancer. Docetaxel, developed later, is used for the management of advanced breast, gastric, NSCLCs, hormone refractory prostate cancer, and advanced head and neck squamous cancer.

Taxane-induced HFS and nail changes. A distinct subtype of HFS has been reported with paclitaxel and docetaxel in 10% and 5% of patients, respectively.⁷⁶ Erythematous plaques develop on the dorsal surfaces of the hands, Achilles tendon, and malleoli, in contrast to the HFS from other chemotherapy drugs which initially develop in the palms and soles. Nail toxicity⁷⁷ (ie, onycholysis, Beau lines, onychomelanosis, and subungual hemorrhage) is also frequent and maybe associated with paronychia (Figs 3 and 4).

Other reactions. Worrisome sequelae from taxanes include hypersensitivity reactions, which can effectively be managed by premedication



Fig 3. Docetaxel-induced nail changes and acral erythema. **A**, Onycholysis and onychomelanosis. **B**, Beau lines and subungual hemorrhage. **C**, Erythematous plaques over photoexposed areas of the hands were observed in a patient after several cycles of docetaxel.

with diphenhydramine and oral steroids. The solvent added with taxanes to enable parenteral administration contributes to the hypersensitivity.⁷⁶

Peripheral sensory neuropathy, myelosuppression (especially neutropenia), fluid retention, and alopecia may also occur from taxanes. Other uncommon cutaneous reactions include radiation recall,^{78,79} photosensitivity,^{80,81} subacute cutaneous lupus erythematosus,⁸² and scleroderma.⁸³

Vincristine, vinblastine, and vinorelbine

Vinca alkaloids were historically extracted from the leaves of the Madagascar periwinkle (*Catharanthus roseus*). Three have been approved for intravenous use in the United States: vincristine, vinblastine, and vinorelbine. Vincristine is often used in combination chemotherapy regimens because of its lack of myelosuppression, and is commonly used to treat acute lymphocytic leukemia, multiple myeloma, chronic lymphocytic leukemia, lymphoblastic crisis of chronic myelogenous anemia, sarcomas, and small cell lung cancer with distant metastases. Indications for vinblastine include testicular cancer and both Hodgkin and non-Hodgkin lymphomas, whereas vinorelbine is approved for unresectable, advanced NSCLC but has also been shown to be helpful for the treatment of advanced breast cancer.⁸⁴

All vinca alkaloids have the potential to cause neuropathy, which is characteristically peripheral, symmetrical, and mixed sensorimotor, as well as a severe autonomic neurotoxicity with constipation, abdominal cramps, ileus, urinary

retention, orthostatic hypotension, and hypertension.⁸⁵ The most effective treatment is discontinuation or a reduction in dose; however, reports of thiamine, vitamin B₁₂, folic acid, pyridoxine, and neuroactive agents have shown variable efficacy.

Alopecia, maculopapular rash,⁸⁶ erythema multiforme-like lesions linearly arranged over the vein after intravenous vinblastine,⁸⁷ and HFS have also been reported.⁸⁸

TOPOISOMERASE INHIBITORS

Key point

- The most common adverse reactions to topoisomerase inhibitors are gastrointestinal disturbance, myelosuppression, hair loss, and hypersensitivity

Topotecan and irinotecan

Topoisomerase inhibitors interrupt DNA synthesis by binding to topoisomerase enzymes, which work to relieve helical strain during DNA replication. The topoisomerase I inhibitors topotecan and irinotecan are water-soluble derivatives of camptothecin, a plant alkaloid from the Chinese tree *Camptotheca acuminata*.⁸⁹ Topotecan has been approved by the US Food and Drug Administration for the intravenous treatment of stage IVB cervical, metastatic ovarian, and small cell lung cancers, but has been shown to have efficacy with multiple other malignancies. Side effects include myelosuppression and gastrointestinal symptoms. Temporary hair loss can also occur 3 to 4 weeks after the first dose. Irinotecan is currently approved only for metastatic colorectal cancer, but like topotecan is used off-label



Fig 4. Taxane-induced nail toxicity. **(A)** Onycholysis and **(B)** paronychia. (Photo courtesy of Mario E. Lacouture, MD, Memorial Sloan Kettering, New York, NY.)

for other cancers. It is also given intravenously, and should be preceded by atropine and a systemic steroid with a serotonin antagonist to minimize cholinergic reactions and emesis. The use of irinotecan is limited by its toxicity, which can be life-threatening. Diarrhea is the most common side effect, followed by myelosuppression.⁹⁰ It has recently been found that patients with the UDP-glucuronosyltransferase gene (*UGT1A1*) *28 allele are at increased risk for adverse effects from irinotecan.⁹¹ Other side effects can include temporary liver dysfunction and reversible hair loss.

Etoposide, teniposide, and amsacrine

Etoposide, teniposide, and amsacrine are inhibitors of the enzyme topoisomerase II, which relieves the helical strain during DNA replication by cutting both strands of DNA simultaneously. Topoisomerase II inhibitors frequently induce rearrangements of the mixed lineage leukemia gene, and can cause a secondary leukemia side effect.⁹² Etoposide has been approved by the US



Fig 5. Hyperpigmentation changes from chemotherapy. (Photo courtesy of Mario E. Lacouture, MD, Memorial Sloan Kettering, New York, NY.)

Food and Drug Administration to be used in combination with other medications to treat small cell lung cancer and testicular cancer. It is a derivative of podophyllotoxin. It is typically taken orally, but can also be administered intravenously, though care must be used to prevent extravasation because it is an irritant and can cause tissue damage. Other cutaneous side effects include HFS, paronychia, hair loss, and perianal irritation.⁹³ Common side effects also include myelosuppression, gastrointestinal distress, hypotension, and a metallic taste. Teniposide is also a podophyllotoxin derivative that has been approved for the treatment of refractory childhood lymphoblastic leukemia. Common side effects include hematologic toxicity, alopecia, nausea/vomiting, and hypersensitivity reaction. Amsacrine is currently approved for the treatment of acute myeloid leukemia. Like etoposide and teniposide, it can cause myelosuppression, alopecia, gastrointestinal distress, and allergic reaction.

PREVENTION AND TREATMENT OF REACTIONS

The prevention and treatment of cutaneous reactions are essential to improve the quality of life of cancer patients and to avoid unnecessary dose modifications that may affect treatment outcome. Immunoglobulin E-mediated hypersensitivity reactions can be best prevented with intradermal testing, when applicable, and premedication with antihistamines and corticosteroids.¹³ A maculopapular rash may easily be treated with topical steroids or a short course of oral steroids for extensive involvement. High potency topical steroids are also useful for HFS and may be combined with topical keratolytics, such as urea and pain relievers.⁴⁴ Cooling of the hands and feet with ice packs both before and during chemotherapy of doxorubicin and taxanes have also been found to reduce HFS and nail changes

through vasoconstriction.^{70,76} For chemotherapy-induced alopecia, the use of topical minoxidil throughout chemotherapy and postchemotherapy may help accelerate hair regrowth after treatment completion.⁴⁴ Hyperpigmentation changes from chemotherapy may also be improved with bleaching agents and sunscreen⁴⁴ (Fig 5).

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Cutaneous reactions to chemotherapeutic drugs and targeted therapies for cancer

Part II. Targeted therapies

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Learning Objectives

After completing this learning activity, participants should be able to identify the mechanism of action of targeted chemotherapeutic drugs, recognize cutaneous

reactions caused by targeted chemotherapeutic drugs, and plan the appropriate management of cutaneous reactions.

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Targeted drugs are increasingly being used for cancer management. They are designed to block specific cancer cell processes, and are often better tolerated than conventional chemotherapeutic drugs. Cutaneous reactions, however, are not uncommon, because some target molecules are also present in the skin. Tyrosine kinase inhibitors can cause edema and macular rash, whereas papulopustular rash, paronychia, regulatory changes in hair, itching, and dryness caused by epidermal growth factor receptor inhibitor (PRIDE) syndrome can be seen in patients treated with these drugs. Vismodegib may result in muscle spasms and alopecia. Multiple rashes can be seen with bortezomib, while sunitinib and sorafenib cause hand–foot skin reactions. New melanoma therapies, such as ipilimumab, cause immune-related adverse events of dermatitis and pruritus, while BRAF inhibitors can produce exanthematous rash and lead to an increased risk of squamous cell carcinoma. Dermatologists should be aware of these new therapies and their cutaneous reactions to be able to provide appropriate care and management for cancer patients. (J Am Acad Dermatol 2014;71:217.e1-11.)

Key words: cancer therapy; chemotherapy; cutaneous reactions; drug hypersensitivity; rash; target drugs.

Targeted therapy blocks the growth and spread of cancer by inhibiting specific molecules involved in tumor pathogenesis. Unlike conventional chemotherapeutic drugs, which act at the cellular level to treat tumors, targeted drugs are theoretically more effective and less harmful to normal cells because specific molecular mechanisms are involved (Table I).¹ Cutaneous reactions to these therapies, however, are not uncommon, because some target molecules (ie, endothelial growth factor receptor [EGFR] and vascular EGFR [VEGFR]) are also present in the skin.² Knowledge of these target drugs and their characteristic patterns of skin reaction is essential for providing proper treatment and care for cancer patients.

SIGNAL TRANSDUCTION INHIBITORS

Key points

- Tyrosine kinase inhibitors for chronic myeloid leukemia may cause edema, hypopigmentation, and a generalized skin rash
- Epidermal growth factor receptor inhibitors can cause papulopustular rash, paronychia, regulatory hair changes, itching, and dryness syndrome
- Vismodegib, which targets the hedgehog pathway in basal cell carcinoma, may produce muscle spasms, alopecia, and dysgeusia

Imatinib, dasatinib, and nilotinib

Imatinib was the first molecule drug developed to inhibit the tyrosine kinases *bcr-abl* in chronic myeloid leukemia, *c-kit* in rare gastrointestinal

Abbreviations used:

EGFR:	epidermal growth factor receptor
EGFRI:	epidermal growth factor receptor inhibitor
HFSR:	hand–foot skin reaction
IRAE:	immune-related adverse event
MAPK:	mitogen-activated protein kinase
PDGFR:	platelet-derived growth factor receptor
PRIDE:	papulopustular rash, paronychia, regulatory hair changes, itching, and dryness caused by epidermal growth factor receptor inhibitors
VEGFR:	vascular endothelial growth factor receptor

stromal tumors, and several platelet-derived growth factor receptors (PDGFRs) in other malignancies.^{3,4} Dasatinib and nilotinib are second-generation tyrosine kinase inhibitors that were developed to treat resistant chronic myeloid leukemia cases with acquired *bcr-abl* mutations.⁴ All are taken orally once or twice daily. Between 7% and 88.9% of patients taking imatinib experience cutaneous reactions^{4,5}; 35% of patients taking dasatinib and 10% to 28% of patients taking nilotinib also have cutaneous reactions.⁴

Edema. Superficial edema is distinct to imatinib, and primarily presents as periorbital edema causing epiphora, conjunctivochalasis, and chemosis.^{3,4} Edema may also occur in the extremities and occasionally as central fluid retention.^{4,5} Dasatinib causes pleural effusions in 30% of patients, while nilotinib rarely induces peripheral edema or pleural effusion.^{6,7} It has been postulated that the inhibition

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Table I. Molecular target of targeted therapy drugs

Drug class	Molecular target
Signal transduction inhibitor	
Multikinase inhibitor	
Imatinib	<i>bcr-abl</i> , <i>c-kit</i> , and PDGFRs
Dasatinib	<i>bcr-abl</i> , <i>c-kit</i> , PDGFRs, Src, and ephrin receptor kinase
Nilotinib	<i>bcr-abl</i> , <i>c-kit</i> , and PDGFRs
EGFR inhibitor	
Gefitinib and erlotinib	Intracellular domain of the EGFR
Cetuximab and panitumumab	Extracellular domain of the EGFR
Vismodegib	Inhibits smoothened (SMO) receptor
Apoptosis-inducing inhibitor	
Bortezomib	Inhibits degradation of kappaB protein and prevents NF-kappaB activation
Angiogenesis-inducing inhibitor	
Sorafenib	Raf, <i>c-kit</i> , PDGFR-b, VEGFRs 2 and 3, FMS-like tyrosine kinase 3 (Flt-3), and RET receptor tyrosine kinase
Sunitinib	VEGFR 1-3, PDGF-a, <i>c-kit</i> , Flt-3, colony stimulating factor-1, and the glial cell line-derived neurotrophic factor receptor
Immunomodulator	
Ipilimumab	CTLA-4
Gene therapy	
Vemurafenib	BRAF V600E
Dabrafenib	BRAF V600E
Trametinib	MEK1 and MEK2

CTLA-4, Cytotoxic lymphocyte antigen-4; EGFR, epidermal growth factor receptor; NF-kappaB, nuclear factor kappaB; PDGFR, platelet-derived growth factor receptor; VEGFR, vascular endothelial growth factor receptor.

of PDGFR produces the increase in dermal interstitial fluid, because PDGFR regulates interstitial fluid homeostasis.⁴ Edema is managed with low salt diet, diuretics, and topical phenylephrine 0.25% ophthalmic drops for periorbital edema.⁴

Maculopapular rash. Kinase inhibitors can produce a dose-dependent maculopapular rash that typically presents over the trunk, forearms, and occasionally the face, but it can rarely progress to a severe exfoliative dermatitis. Patients can be managed with topical or oral steroids and antihistamines.^{4,5}

Pigmentary changes. Localized, patchy, or diffuse hypopigmentation and depigmentation can occur with kinase inhibitors, though more often in patients with darker skin.⁵ In 2 studies, 41% of 118 patients⁸ and 33% of 24 patients⁹ taking imatinib had depigmentation. These pigment changes are caused by the inhibition of *c-kit*, a protein that regulates melanocyte development, migration, and survival,⁴ and are usually reversible with dose reduction or discontinuation. Hyperpigmentation, on the other hand, has been observed in only 3.6% of patients treated with kinase inhibitors.⁵ It can occur in the nails, hair, oral mucosa and, in 1 case report, on the back.⁴ Pigmentation may be caused by the deposition of drug metabolites containing melanin and iron, similar to that caused by minocycline and antimalarial drugs.¹⁰

Other reactions. Urticular, lichenoid, pityriasisiform, and psoriasisiform rashes may occur. Severe reactions reported include Stevens–Johnson syndrome, acute and generalized exanthematous pustulosis, Sweet syndrome, neutrophilic eccrine hidradenitis, and neutrophilic panniculitis. Rarely reported effects include mycosis fungoides-like reaction, follicular mucinosis, Epstein–Barr virus-positive B cell lymphoproliferative tumor, hyaline cell syringoma, malpighian epithelioma, porphyria cutanea tarda, and pseudoporphyria.⁴

Skin reactions that commonly occur with dasatinib include pruritus, acne, xerosis, hyperhidrosis, urticaria, and eczema. Other rare side effects that have been reported are pigmentary changes, skin ulcers, bullous disorder, photosensitivity, nail disorder, acute febrile neutrophilic dermatosis, panniculitis, and palmoplantar erythrodysesthesia syndrome. Cutaneous reactions to nilotinib include xerosis, alopecia, and bullous Sweet syndrome.⁴

Gefitinib, erlotinib, cetuximab, and panitumumab

EGFR inhibitors (EGFRIs) block the signal transduction pathway needed for cell proliferation, migration, and angiogenesis of tumor cells. Gefitinib and erlotinib are orally administered EGFR tyrosine kinase inhibitors, while cetuximab and



Fig 1. Acneiform eruption. Papulopustular lesions on the (A) chest, (B) scalp, and (C) face of a patient who was taking an epidermal growth factor receptor inhibitor.

panitumumab are humanized monoclonal antibodies that are given intravenously. These drugs are used for colorectal cancer, breast cancer, pancreatic cancer, non–small cell lung cancer, and head and neck squamous cell carcinoma (SCC).¹¹ Skin reactions are common because EGFRs are expressed in basal keratinocytes, sebocytes, outer root sheath, and endothelial cells. Common reactions can be summarized by the *papulopustular* rash, paronychia, regulatory changes in hair, *itching*, and *dryness* caused by EGFRIs (PRIDE) syndrome.^{3,12}

Papulopustular rash. This rash appears about a week after initiating EGFRi therapy, and occurs in 24% to 62% of patients taking gefitinib, 49% to 67% of patients taking erlotinib, and 75% to 91% of patients taking cetuximab.³ The rash has been found, in some studies, to be directly correlated to the therapeutic efficacy of EGFRIs and an increase in survival. However, there have also been a number of studies that failed to correlate the rash response with therapeutic outcome.¹² The acneiform eruption affects the scalp, face, chest, back

and, less commonly, the extremities, lower back, and abdomen (Figs 1 and 2).^{3,11} The histopathologic results reveal a superficial inflammatory cell infiltrate surrounding hyperkeratotic follicular infundibula or a florid neutrophilic suppurative folliculitis with a rupture of the epithelial lining.¹² The lesions are acneiform, but benzoyl peroxide or topical tretinoin should not be recommended because they irritate and dry the skin. Mild cases can be treated with medium to high potency topical steroids, topical clindamycin, or erythromycin; oral minocycline and doxycycline are recommended for more advanced cases.¹² Systemic isotretinoin can be useful in cases that are not responsive to antibiotic therapy.¹³

Paronychia. The second most common reaction to EGFRIs occurs in the nails and digits, with the first digit being the most commonly affected. Reactions may present as nail discoloration, pitting, paronychia, periungual pyogenic granuloma, cracked and swollen nail folds and cuticles, ingrowth of nails, and the partial or complete loss of nails (Fig 3). These appear 1 to 2 months after beginning treatment and occur in 10% to 15% of patients.³ When secondary infection occurs, culture swabs are recommended. In a retrospective study of cetuximab patients with paronychia, 23% had *Staphylococcus aureus* infections and 31% had coagulase-negative, Gram-positive bacteria (nosocomial colonization). Antibacterial soaks (diluted bleach or vinegar in water) are recommended to prevent superinfection. Warm compresses, silver nitrate,¹⁴ topical corticosteroids, and systemic tetracyclines may also be used to reduce periungual inflammation.¹²

Regulatory hair changes. Hair may become finer, brittle, curled, or slow in growth, and alopecia may follow several months into therapy. Hypertrichosis, facial hirsutism, and trichomegaly may also occur. Patients can be reassured that these hair changes are temporary; normal growth should begin within 1 month after cessation of medication.^{3,12}

Itchiness. Pruritus occurs in approximately half of patients, and has a large impact on quality of life. Gentle skin care using cool or lukewarm baths (instead of hot showers), mild soap, fragrance- and alcohol-free emollients, sunscreens, and sun avoidance are advised. Systemic antihistamines, doxepin, pregabalin, and gabapentin may also be given for relief of itchiness.¹²

Dryness. Xerosis results from abnormal keratinocyte differentiation, leading to a deteriorated stratum corneum, a decrease in epidermal loricrin, and a decrease in moisture retention.¹² Dryness appears over time and is reported in 35% of patients. Severe xerosis may result in asteatotic eczema and acral

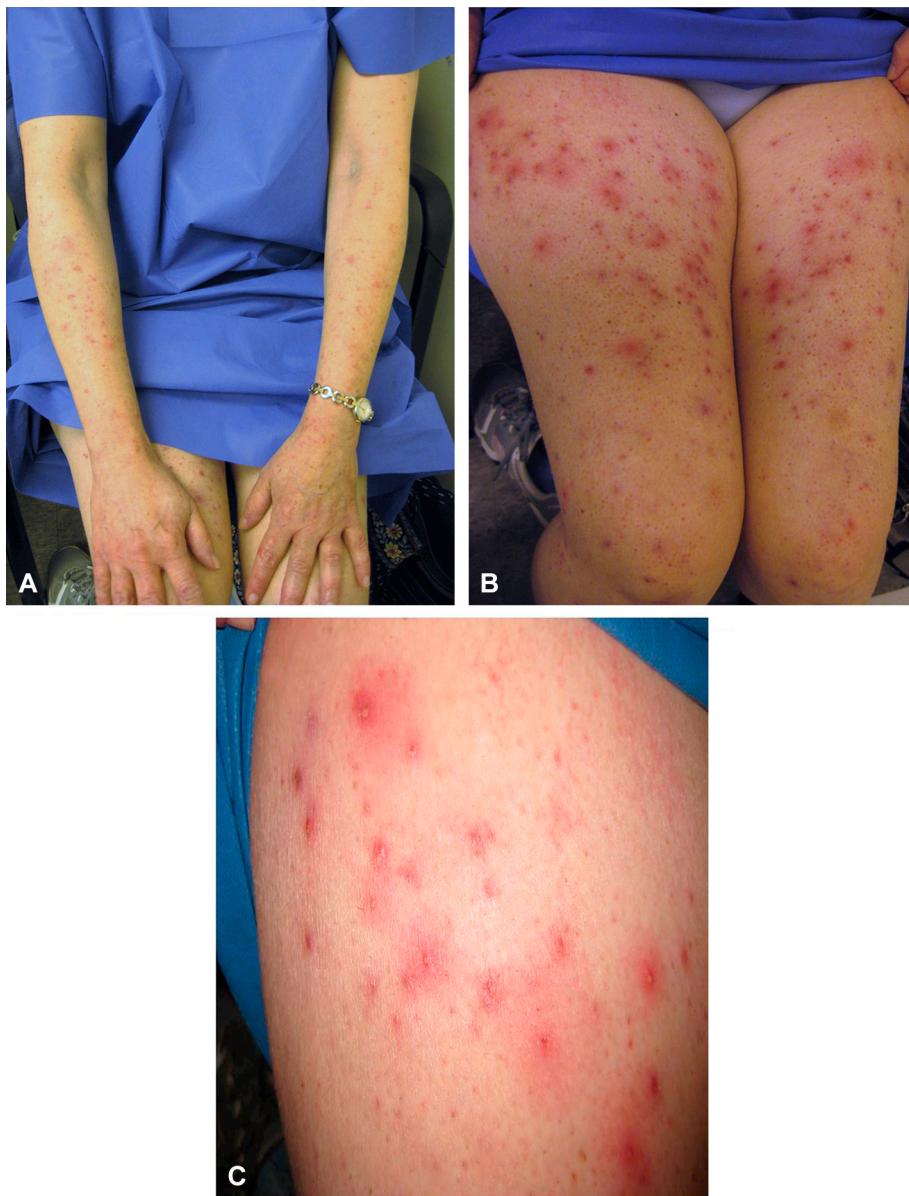


Fig 2. Acneiform eruption. Papulopustular rash over the (A) arms and (B) legs of a patient who was taking an epidermal growth factor receptor inhibitor. C, Close view of follicular papules on the thigh.

fissures.¹¹ Bathing using tepid water and mild soap are advised. For fissures, protective covering for the feet and hands help prevent additional skin injury and promote healing.¹²

Other reactions. Anaphylaxis occurs in 1.2% to 3.5% of patients taking cetuximab and 1% of patients taking panitumumab.³ Interestingly, a higher incidence of cetuximab anaphylaxis (22%) has been observed in Tennessee and North Carolina.¹⁵ Serum analysis found that 20% of subjects from Tennessee, 6.1% of subjects from North Carolina, and only 0.6% of control subjects from Boston have immunoglobulin E antibodies against cetuximab.¹⁶

Other reactions to EGFRIs include enhancement of radiation dermatitis, oral aphthous ulcers,¹⁷ ocular complications (ie, dry eye and corneal abrasions),¹⁸ vasculitis,¹² necrolytic migratory erythema,¹⁹ and transient acantholytic dermatosis.²⁰

Vismodegib

Vismodegib is a small-molecule inhibitor of the smoothened receptor, which prevents activation of the hedgehog pathway required in basal cell carcinoma pathogenesis. It has been approved by the US Food and Drug Administration for the treatment of metastatic basal cell carcinoma and



Fig 3. Paronychia. Cracked and swollen nail folds and cuticles and periungual pyogenic granuloma associated with epidermal growth factor receptor inhibitor treatment.

locally advanced basal cell carcinoma that has recurred after surgery or cannot be treated with surgery or radiation.²¹ It was shown to have a 58% response during its phase II clinical trials, and 54% of patients with locally advanced disease had no residual carcinoma found in biopsy specimens.²² The medication is taken orally daily, and is recommended to be continued until disease progression or intolerable toxicity. In the phase II trials, it was reported that all subjects experienced at least 1 side effect, with 25% experiencing serious toxicity.²³ Muscle spasms were the most commonly experienced (68%), followed by alopecia (63%), dysgeusia (51%), fatigue, nausea, anorexia, and diarrhea.²³

APOPTOSIS-INDUCING INHIBITORS

Key point

- **Bortezomib causes different forms of skin rash because of the enhanced release of proinflammatory cytokines**

Bortezomib

Bortezomib is a proteasome inhibitor that prevents nuclear factor kappaB activation and induces apoptosis of malignant cells.²⁴ It has been used in the treatment of multiple myeloma,²⁵ non-Hodgkin lymphoma, and mantle cell lymphoma, and its most common side effects are gastrointestinal distress and weakness, but peripheral neuropathy and myelosuppression are also frequently encountered.²⁶ It is given in 2- to 6-week cycles of once or twice weekly intravenous or subcutaneous doses.

Cutaneous reactions secondary to bortezomib affect 10% to 24% of patients, and are variable in presentation.²⁵⁻²⁷ The exact pathogenesis is unclear, but it is hypothesized that bortezomib enhances the release of proinflammatory cytokines, causing a rash.²⁵ In 1 study, 6 of 47 multiple myeloma patients developed cutaneous lesions with bortezomib

(erythematous nodules and plaques in 5 patients and a morbilliform rash with ulcers in 1 patient).²⁶ In another study, 26 of 140 patients with non-Hodgkin lymphoma had different forms of rash, with papules and nodules being the most common presentation.²⁷ Histopathology of these reactions is also diverse; perivascular dermatitis, interface dermatitis, and leukocytoclastic vasculitis have all been described. Most cutaneous reactions to bortezomib occur during the third or fourth treatment cycle, with the rash appearing within the first few days and resolving 5 to 7 days after the last dose in the cycle or with treatment with antihistamines and prednisone. Subcutaneous administration appears to be associated with fewer overall side effects,²⁷ but injection site reactions have been reported to occur in 51% to 57% of patients.²⁸

Sweet syndrome secondary to bortezomib has also been reported.^{29,30} The lesions appeared on the first and second cycles of therapy, and disappeared spontaneously or after discontinuation of bortezomib. Systemic corticosteroids given during subsequent cycles prevented recurrences for these patients.

ANGIOGENESIS-INDUCING INHIBITORS

Key points

- **Inhibitors of angiogenesis primarily cause localized patches of hand–foot skin reactions, but face, hair, nail, and oral reactions may also occur**
- **Sunitinib may cause yellowing of the skin, while sorafenib may cause squamous cell carcinoma or actinic keratosis eruptions**

Sorafenib and sunitinib

Sorafenib and sunitinib are multikinase inhibitors that specifically target tumor cell angiogenesis and proliferation via VEGFR, PDGFR, and other kinases.³¹ Sorafenib is used for the treatment of renal cell carcinoma, hepatocellular carcinoma, melanoma, non–small cell lung cancer, pancreatic cancer, and colon cancer.³ Sunitinib is approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumor, colon cancer, and breast cancer.³¹ Both are taken orally.

Cutaneous reactions to multikinase inhibitors are common, and in a prospective study, were found to occur in 74% of patients taking sorafenib and 81% of patients taking sunitinib.³² Hand–foot skin reactions (HFSRs) and stomatitis are the most frequently encountered side effects. The cause of these reactions is unknown, but it has been postulated to be the result of vessel damage by either VEGFR and PDGFR inhibition, or the extravasated drug itself.³¹



Fig 4. Hand-foot skin reaction in a patient taking sunitinib, with hyperkeratotic lesions on the palms (**A**) and soles (**B**). (Photography courtesy of Richard Johnson, MD.)

HFSRs. HFSRs appear in 10% to 62% of patients taking sorafenib and 10% to 28% of patients taking sunitinib (Fig 4).³³ It presents differently from hand–foot syndrome caused by conventional chemotherapy, which is a symmetrical, well demarcated palmoplantar erythema that can blister and ulcerate. Instead, painful localized patches develop on friction and trauma-prone areas, such as the heel, lateral aspects of the soles, and web spaces. Lesions appear during the first 2 to 4 weeks of treatment and are hyperkeratotic with superficial blistering and occasional erythematous halos.³¹ Biopsy specimens reveal acanthosis, parakeratosis, and dyskeratosis with a dense superficial perivascular lymphocytic infiltrate in the dermis.³¹

Lacouture et al³⁴ proposed treatment recommendations based on grading. Grade 1 reactions with minimal skin changes require supportive management, such as protective gloves and footwear to

minimize friction, and the use of topical keratolytic medications, such as urea or tazarotene. Grade 2 reactions, which include painful skin changes that limit activities of daily living (ADL), can be treated with pregabalin or nonsteroidal drugs to help with pain, topical clobetasol, and topical lidocaine, and a 50% reduction in dose for 1 to 4 weeks. Grade 3 reactions are severe skin changes with limited self-care ADLs that need a dose interruption of at least 1 week or until symptoms become minimal.

Oral complications. Stomatitis is the second most common cutaneous reaction from treatment with sorafenib (26%) and sunitinib (36%).³² Oral lesions appear early in the course of treatment and directly correlate to the severity of HFSR. The management of oral complications is limited and includes good oral hygiene and the use of topical steroids, local anesthetics, and antibacterials.³⁵

Hair. Alopecia begins 2 to 28 weeks after the onset of therapy, and occurs in 26% of patients taking sorafenib and 6% of patients taking sunitinib.^{31,32} With sorafenib, new hair may grow during treatment, but it becomes brittle, curly, and pigmented. Sunitinib, on the other hand, causes depigmentation of hair in 10% of patients through effects on stem cell growth factor receptor signaling, which modulates the genes encoding tyrosinase. Depigmentation occurs after 5 to 6 weeks of treatment and returns to normal 2 to 3 weeks after cessation of sunitinib. Interestingly, in patients with intermittent dosing, there is development of alternating bands of depigmented and pigmented hair.³¹

Face. Facial erythema resembling seborrheic dermatitis has been noted in 63% of patients taking sorafenib and, to a lesser extent, with sunitinib.^{31,32} It appears early in the course of treatment and resolves <2 months after drug discontinuation. Scalp dysesthesia has been found to occur in almost half of patients treated, which spontaneously resolves even if treatment continues.³⁶ Facial edema, especially on the eyelids, may also occur in 24% of patients receiving sunitinib, and may be caused by increased vascular permeability and fluid retention from PDGFR inhibition.^{31,32}

Nails. Fingernail subungual splinter hemorrhages develop in 70% of patients taking sorafenib and 25% of patients taking sunitinib.^{31,32} They present during the first 2 months of therapy and resolve spontaneously without treatment. It is hypothesized that the inhibition of VEGFR by sorafenib and sunitinib may play a role in the renewal of capillaries that sustain frequent injuries at the distal fingers.³

Skin pigment. Yellow skin pigmentation occurs in 28% of patients taking sunitinib, usually on the

face, with sparing of the sclera and oral mucosa. It is typically noticed after the first to fourth weeks of treatment, and resolves once treatment is discontinued. This discoloration is caused by the yellow color of sunitinib and its metabolites, and has also been noted to affect the urine.^{31,32}

Skin cancer. The development of new SCCs and inflammation of existing actinic keratoses have been known to be associated with sorafenib in 10% of patients. HRAS, TGFBR1, and TP53 oncogenic mutations have been detected in these lesions, leading to the hypothesis that sorafenib may increase keratinocyte proliferation and mitogen-activated protein kinase (MAPK) pathway activation in normal skin, with ultraviolet light-induced mutations likely influencing the evolution of benign lesions to more proliferative and malignant tumors.^{37,38}

Other reactions. Other cutaneous reactions to sorafenib include reports of generalized keratosis pilaris-like eruption (21%), body alopecia (19%), nipple hyperkeratosis or pain (19%), and epidermal cysts (5%).^{31,32,36} There have also been single reports of erythema multiforme-like eruption,³⁹ ultraviolet radiation recall,⁴⁰ and localized dyskeratotic plaque with milia.⁴¹ Single cases of benign eruptive melanocytic nevi⁴² and drug-induced lentigenes^{31,32} have been reported secondary to sorafenib and may be related to its inhibition of BRAF or BRAF V600E.

IMMUNOMODULATORS

Key point

- **Ipilimumab can cause immune-related adverse events, such as dermatitis, pruritus, enterocolitis, and hepatitis**

Ipilimumab

Ipilimumab is an immune-modifying monoclonal antibody that promotes unrestrained T cell activation against tumor cells. It has been approved by the US Food and Drug Administration as an intravenous treatment for metastatic melanoma, and current trials have shown efficacy in the treatment of ovarian cancer, prostate cancer, and metastatic renal cancer.⁴³

Side effects are characteristically called immune-related adverse events (IRAEs) and represent tolerance to self-antigens.⁴³ IRAEs affect 64.2% of patients, with serious IRAEs occurring in 10% to 15% of these patients. Dermatitis, pruritus, enterocolitis, and hepatitis are the most common IRAEs; less common reactions include hypophysitis, uveitis, iridocyclitis, neuropathy, and Guillain–Barré syndrome.^{44,45} Cutaneous reactions usually occur 3 to 4 weeks after drug initiation, followed by gastrointestinal and hepatic reactions 6 to 7 weeks

afterward, then endocrine side effects at 9.2 weeks after drug onset.⁴⁶ These reactions are dose-dependent and have been reported to correlate with the clinical efficacy of ipilimumab.

Dermatitis and pruritus affect 47% to 68% of patients, but severe reactions were found to affect only 4% of patients in a pooled analysis of 325 patients receiving ipilimumab.⁴⁶ The pruritic exanthema is distributed over the proximal extensors, trunk, and sometimes head,⁴⁷ and is accompanied by a peripheral blood eosinophilia. Histologic studies of the rash have shown a perivascular CD4⁺ predominant lymphocytic infiltrate with eosinophils in the dermis, rare dyskeratotic cells, and mild spongiosis,⁴⁷ while immunohistochemistry studies found CD4⁺ and Melan-A-specific CD8⁺ T cells near apoptotic melanocytes.⁴⁷

The management of rash depends on the severity. Generally, it resolves with the use of topical corticosteroid cream without the need to reduce or interrupt treatment. Topical urea in combination with polidocanol, an antipruritic agent, has also been recommended.⁴⁶ With severe cutaneous reactions, systemic corticosteroids, such as prednisone 1 to 2 mg/kg, are given, and ipilimumab should be discontinued when necrotic, bullous, or hemorrhagic lesions are present. Rarely, severe, life-threatening cutaneous reactions may occur; there has been 1 report of toxic epidermal necrolysis.⁴⁸

GENE THERAPY

Key points

- **BRAF inhibitors may cause skin toxicities via the inhibition of the mitogen-activated protein kinase pathway in keratinocytes**
- **Preliminary studies combining MEK and BRAF inhibitors show a potential decrease in the incidence of skin toxicity and squamous cell carcinoma**

Vemurafenib and dabrafenib

Genetic mutations in the MAPK pathway (RAS-RAF-MEK-ERK mitogen-activated protein kinase pathway) are present in >80% of cutaneous melanomas, with the most common mutation in BRAF V600E. Vemurafenib and dabrafenib selectively inhibit the BRAF V600E oncoprotein, thereby inhibiting this pathway that is important in melanoma tumorigenesis.⁴⁹ Both medications are taken orally with twice daily dosing.

BRAF inhibitors are generally well tolerated by patients, and have significantly shown efficacy and improved survival rates in several drug trials. Noncutaneous adverse reactions to BRAF inhibitors

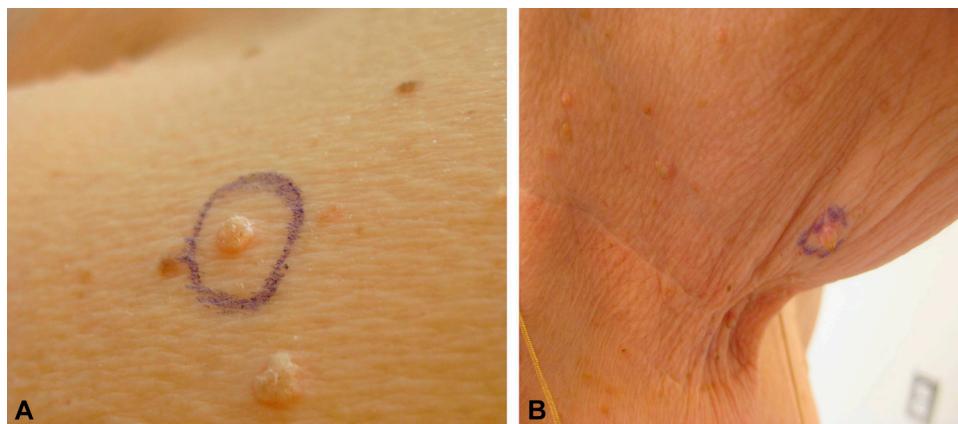


Fig 5. Verrucous keratosis. Hyperkeratotic lesions on the (A) arm and (B) neck in a patient undergoing BRAF inhibitor therapy.

include arthralgias, fatigue, nausea, diarrhea, and pyrexia.⁵⁰ Cutaneous reactions are the most common toxicity to BRAF inhibitors, affecting 74% of patients. Reactions are similar to adverse events caused by EGFRIs, which may be because RAF is a major mediator in EGFR signaling pathways. Inhibition of the MAPK pathway in keratinocytes can result in keratinocyte cell death, decreased cell migration, and inflammation causing dermatologic side effects.⁵⁰

Exanthematous rash. Multicenter trials studying the BRAF inhibitors have shown that rash affects 15% to 18% of patients taking vemurafenib^{51,52} and 27% of patients taking dabrafenib.⁵³ This reaction is dose-dependent, and its morphology is commonly papulopustular, occurring on the face, torso, and arms. The lesions appear in the first few months of therapy and clear with dose interruption or reduction. As with EGFR reactions, topical steroids and topical antibiotics can be used in mild cases, with systemic tetracyclines recommended for more advanced cases and oral prednisone or retinoids reserved for resistant and/or severe rashes.⁵¹

Keratotic lesions. In patients treated with vemurafenib and dabrafenib, 12% and 8% have been reported to develop cutaneous SCC and keratoacanthoma, respectively.⁵¹ Most growths appear 2 to 14 weeks from treatment, and SCC and keratoacanthoma represent the most common neoplasms. Treatment is by excision, and dose modification is not required. It is advised, however, that patients taking BRAF inhibitors have a thorough dermatologic examination at baseline and regular follow-up for the development of new skin lesions. Benign keratotic lesions can also be found, and several studies have shown that verrucous keratosis is the most common manifestation.^{54,55} Other noncancerous growths can include acantholytic

dermatosis, seborrheic keratosis, verruca vulgaris, and hypertrophic actinic keratosis.⁵⁴

Photosensitivity. Photosensitivity has been shown to occur in 7% to 12% of patients taking vemurafenib.^{51,52} Patients reported a burning sensation after 10 minutes of ultraviolet A light exposure.⁵⁶ Broad-spectrum sunscreens and ultraviolet light protective clothing are routinely advised for patients.

Other reactions. Dry skin, pruritus, fissures, and paronychia can develop with prolonged administration of BRAF inhibitors, such as in those who have had >3 months of treatment.⁵⁰ Alopecia was reported in 8% to 36% of patients, as were several other hair follicle changes.⁵⁷ Plantar hyperkeratosis occurs in 9% to 10% of patients taking vemurafenib and 20% of patients taking dabrafenib.⁵⁷ Hyperkeratosis occurs in 8% to 29% of patients taking vemurafenib and 27% to 49% of patients taking dabrafenib (Fig 5).^{50,57} Panniculitis with arthralgia caused by BRAF inhibitors has also been reported.⁵⁸

Trametinib

MEK inhibitors are potent and selective allosteric inhibitors of MEK1 and MEK2 of the MAPK pathway. The MEK inhibitor trametinib has been approved as an oral daily treatment of metastatic or unresectable melanoma with BRAF V600E or V600K gene mutation.

Several studies have combined trametinib with BRAF inhibitors in phase I/II trials for melanoma, and showed potential reduction in BRAF inhibitor resistance and a decreased incidence of SCC side effects.^{49,50} Another study involving 43 melanoma patients showed 20% with skin toxicity, 6% with exanthems, and none reported SCCs or other hyperproliferative skin lesions.⁵⁹ In a study of 109 patients, only 13% reported exanthema and <1% reported squamous cell carcinoma.⁶⁰

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Answers to CME examination

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Evaluation and diagnosis of the hair loss patient

Part I. History and clinical examination

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Learning Objectives

After completing this learning activity, participants should be able to describe how to take an appropriate history and perform clinical examination when diagnosing different types of hair disorders.

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Hair loss (alopecia) is a common problem and is often a major source of distress for patients. The differential diagnosis of alopecia includes both scarring and nonscarring alopecias. In addition, many hair shaft disorders can produce hair shaft fragility, resulting in different patterns of alopecia. Therefore, an organized and systematic approach is needed to accurately address patients' complaints to achieve the correct diagnosis. Part 1 of this 2-part continuing medical education article on alopecia describes history taking and the clinical examination of different hair loss disorders. It also provides an algorithmic diagnostic approach based on the most recent knowledge about different types of alopecia. (*J Am Acad Dermatol* 2014;71:415.e1-15.)

Key words: alopecia areata; androgenetic alopecia; discoid lupus erythematosus; dissecting cellulitis; hair; lichen planopilaris; patterned hair loss; telogen effluvium; trichoscopy.

HISTORY

Key points

- Hair shedding is a major source of psychological distress to patients
- Different hair disorders are more common in certain age groups

Considerable psychological distress usually accompanies patients presenting with hair shedding.¹⁻³ Spending the first portion of the consultation listening to the patient's concerns without actively directing the consultation can help relieve fear and establish a good rapport. The patient's age is important. Certain diseases are more common in children compared to adults. Alopecia areata (AA) and tinea capitis are the 2 most common hair loss disorders in children.⁴ Trichotillomania typically has a prepubertal to young adulthood age of onset.⁵ Traction alopecia can begin during childhood, but the prevalence is highest among young adult women.⁶ Patterned hair loss (PHL) usually has a postpubertal age of onset. Frontal fibrosing alopecia (FFA) is more common in postmenopausal women⁷ (Table I).

CAPSULE SUMMARY

- Hair loss (alopecia) is a common problem and is often a major source of distress for patients.
- The differential diagnosis of alopecia includes both scarring and nonscarring alopecias.
- A successful systematic approach for diagnosing different types of alopecia should follow the classical clinical steps: history, clinical examination, use of trichoscopy, and laboratory investigation.

PRIMARY COMPLAINT AND DURATION

Key points

- Hair thinning and hair shedding are the 2 primary hair-related complaints reported to dermatologists
- Scalp hair thinning only becomes noticeable after losing >50% of the normal scalp hair density
- The duration of hair loss might give a clue to the possible diagnosis and can have a prognostic value

Progressive thinning and excessive shedding of the scalp hair are the 2 most common hair complaints reported to dermatologists. In the former, patients usually report a decrease in hair coverage to the level that they cannot hide their scalp. Consequently, maintaining their usual hairstyle may become impossible. Females may report a significant change in the size of their ponytails. Fifty percent of scalp hair is typically lost before diffuse hair thinning becomes noticeable to the patient.⁸ Progressive thinning of the scalp hair classically occurs in PHL.⁹ Less common causes include primary scarring alopecias, such as

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Table I. History of hair loss checklist

Duration	
Thinning	
Shedding	
Pattern of hair loss	
Diffuse	
Localized	
Associated symptoms	
Itching	
Pain	
Burning	
Present health and medical history	
Drug history	
Nutritional history	
Psychosocial history	
History of hair care practices/use of hair cosmetics	
Family history	
Androgen excess (in women)	

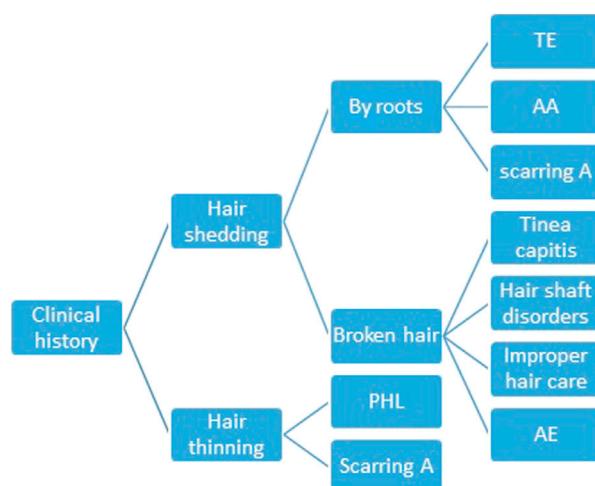


Fig 1. Differential diagnosis of the 2 most common hair complaints. *A*, Alopecia; *AA*, alopecia areata; *AE*, anagen effluvium; *PHL*, patterned hair loss; *TE*, telogen effluvium.

lichen planopilaris (LPP), pseudopelade of Brocq, and fibrosing alopecia in a pattern distribution.¹⁰ Other inflammatory scalp conditions, such as psoriasis and seborrheic dermatitis of the scalp, can also lead to progressive thinning of the scalp hair^{11,12} (Fig 1).

On the other hand, hair may fall out in clumps, especially during shampooing or combing. Key questions implicating significant hair shedding are hairs on the patient's pillows and hairs in food and on the kitchen counter and stove—assuming that the patient cooks. Normally, up to 100 telogen hairs can be lost daily.⁸ Excessive shedding of scalp hair usually indicates telogen effluvium (TE). However, it may also occur in AA or during active stages of different types of scarring alopecia^{1,4,10} (Table II).

Changes in hair texture, such as becoming frizzier or curlier, are not unusual complaints. These changes can occur in PHL.⁹ Similarly, end-stage scarring alopecia may produce tufts of hairs that are curly and kinky.^{10,13} Significantly slower rates of hair growth or complete cessation of hair growth past a certain length are 2 complaints that may be labeled as nonspecific by many dermatologists. While the former can occur in PHL and reflects changes in hair cell cycling dynamics—in which the anagen phase becomes shorter and the telogen phase becomes longer—the latter usually occurs in disorders with hair shaft fragility or in short anagen syndrome.^{14,15} In children, kinky or nongrowing hair should lead clinicians to consider hair shaft disorders.^{16,17}

Distinguishing the hair that is shed by the roots versus breaking is of great importance. Each type has a different differential diagnosis (Table III).

It is important to ask your patients whether regrowth of hair in the affected areas has ever occurred. Regrowth of hair typically occurs in non-scarring alopecias.⁸ However, it can rarely occur in very early treated scarring alopecia¹⁸ (Fig 2).

The duration of hair loss might give a clue to the possible diagnosis and, in addition, have a prognostic value. Acute TE, which occurs in response to a variety of triggers, usually lasts for <6 months. On the other hand, PHL, hair fragility caused by hair shaft disorders, and most scarring alopecias are chronic disorders. AA is a completely unpredictable disease.⁴ Spontaneous hair regrowth has been reported in up to 55% of cases within 1 year.⁴ Long-lasting AA usually has an unfavorable prognosis.^{4,19}

PATTERN OF HAIR LOSS

Key points

- Diffuse scalp hair thinning is typically seen in TE and in rare occasions of acute diffuse AA
- Localized hair thinning to the frontal and the crown regions of the scalp is typically seen in PHL
- Patchy hair loss pattern classically occurs in AA

Recognizing the pattern of hair thinning or shedding is helpful. Diffuse thinning of the scalp hair including both temporal regions is highly suggestive of TE.¹ Localized hair thinning predominantly involving the frontal and the crown regions of the scalp is typical in patients with PHL. FFA almost exclusively affects the frontal and frontotemporal hairlines.⁷ The periphery of the scalp is usually involved in cases of traction alopecia.⁶ Central

Table II. Nonscarring alopecias: Clinical features of the most common types

Characteristics	History	Clinical examination				Hair card
		Global appearance	Hair shedding	Pull test		
Patterned hair loss	Age: puberty or older Onset: gradual Possible FHx	Hair thinning with or without bare patches Distribution: men—the crown, receding hairline; women—wider midline part of the crown	Minimal	Usually negative; if positive: frontal > occipital (telogen hair)	Miniatuerized hair in affected areas	
Telogen effluvium	Age: mostly adults Onset: abrupt May be triggered by iron deficiency, thyroid imbalance, general anesthesia, postpartum, and drugs	Hair thinning No bare patches Distribution: generalized	Prominent	Positive: telogen hair	Hair regrowth in recovering disease	
Alopecia areata	Age: mostly before 20 years of age Onset: abrupt May have personal or FHx of autoimmune disease	Mostly bare patches; rarely diffuse hair thinning Distribution: patchy or multifocal	Prominent	Positive: dystrophic anagen hairs ⁴	Exclamation point hairs indicates active disease states	
Tinea capitis	Age: mostly children Onset: gradual or abrupt Contact with animals (eg, pets)	Total alopecia in 5% of cases ⁴ Bare patches Distribution: any area of scalp; focal or multifocal with or without inflammation; scales	Prominent	Positive: may be broken hairs	Broken hairs	
Trichotillomania	Age: mostly children and adolescents ⁵ Onset: gradual or abrupt Feeling a tension that is relieved by pulling the hair Can be associated with other psychiatric disorders	Hair thinning Rarely bare patches Distribution: frontotemporal/ frontoparietal scalps Bizarre shaped patches with irregular borders	Minimal	Negative	Broken hair Different hair lengths	

FHx, Family history.

Table III. Hair shedding: Differential diagnosis

Hair coming out by the roots
Telogen effluvium
Alopecia areata
Pattered hair loss
Drugs
Loose anagen syndrome
Hair breakage
Tinea capitis
Trichotillomania
Improper hair care practices/hair care cosmetics
Structural hair shaft disorders
Anagen effluvium

centrifugal cicatricial alopecia (CCCA) typically starts at the vertex of the scalp and expands centrifugally.^{10,20} AA can present in many different patterns. The patchy type is usually localized; however, a more diffuse pattern has also been recognized.^{4,19} Generalized total body hair shedding can occur in AA universalis. Trichotillomania usually has a bizarre pattern of scalp or body hair involvement.⁵ On occasion, other hairy body areas can also be affected in multiple scarring and nonscarring alopecic conditions. Graham Little—Piccardi—Lassueur syndrome is a condition in which LPP of the scalp hair is associated with nonscarring hair loss of axilla and groin and follicular spinous papules of the body or the scalp.^{21,22}

SCALP ITCHING AND SORENESS

Key point

- Changes in scalp symptoms can be used to predict disease flare-up and monitor the response to therapy

Soreness, itching, and a burning sensation of the scalp can frequently occur in different types of scarring alopecia and, less commonly, in nonscarring alopecias.^{9,20,23} Trichodynia, a scalp paresthesia, is not infrequent in PHL.²⁴ Trichodynia may correlate with emotional distress related to the hair loss rather than the actual hair loss.²⁴ Changes of these symptoms over the disease course can be used to predict disease flare-ups, especially in scarring alopecia, and to monitor the response to therapy.^{7,10,20}

PRESENT HEALTH AND MEDICAL HISTORY

Key points

- A variety of autoimmune, metabolic, and endocrine disorders can cause different types of hair loss



Fig 2. Alopecia areata presenting with a well-defined patch on the temporal scalp and showing spontaneous regrowth of hair.

- The medical and surgical history—especially for the 6-month period before the onset of hair loss—can be related to the cause

A variety of different health conditions can cause hair loss. The patient's medical and surgical history—especially during the 6-month period before the onset of the hair loss—is of paramount importance. Endocrine disorders, autoimmune diseases, high fever, severe sickness, surgeries under general anesthesia, pregnancy, crash dieting, and sudden weight loss can all trigger TE. Patients should be screened for symptoms of hypo- and hyperthyroidism.¹ Systemic lupus erythematosus (SLE) can cause both scarring and nonscarring alopecia.²¹ In addition to lupus-induced TE, lupus hair is another nonscarring alopecia that presents with dry and coarse hair involving predominantly the frontal hairline.²¹ On the other hand, discoid lupus erythematosus (DLE) is a scarring alopecia that usually affects the scalp and sun-exposed skin. Symptoms such as photosensitivity, mouth ulcers, and joint pain should always be reviewed in such cases.^{10,21,25} In children, congenital hair shaft disorders can be associated with many cutaneous and extracutaneous manifestations; eczema, ichthyosis, nail and teeth anomalies, and neurologic symptoms should be evaluated.^{16,26}

Finally, ask about patient's height and weight and then make a note of the patient's body mass index. Women with polycystic ovarian syndrome (PCOS) can frequently be overweight.^{27,28}

DRUG HISTORY

Key points

- Drug-induced alopecia is usually diffuse and nonscarring
- Identifying a compatible chronology of drug exposure and the onset of hair loss is the key to diagnose drug-induced alopecia

A subtle to very noticeable hair loss can be caused by different types of drugs. Drug-induced alopecia is usually diffuse and nonscarring. TE, anagen effluvium (AE), and accentuation of PHL by androgens are the primary mechanisms by which this hair loss entity occurs.^{29,30} Scalp hair is typically affected; however, the eyebrows, beard, axillary, and pubic and body hair can also be involved. In drug-induced TE, increased shedding of the scalp hair occurs 2 to 3 months after initiation of the offending drug.³⁰ Mood stabilizers (eg, lithium and sodium valproate) and certain antidepressants (eg, fluoxetine) are among the possible causes. Other causes include anticoagulants (eg, warfarin and enoxaparin), beta-adrenoceptor antagonists (eg, metoprolol and propranolol), retinoids, and antimicrobial and anti-viral medications (eg, isoniazid and indinavir).³⁰⁻³² The interruption of long-term estrogen-containing oral contraceptives can also lead to TE.³³ On the other hand, AE is the type of hair loss that follows the administration of certain antineoplastic medications. Alkylating agents, antimetabolites, and vinca alkaloids can suddenly shut off the mitotic activity in rapidly dividing matrix cells of the anagen hair follicles, leading to hair fiber breakage.^{34,35} AE usually results in a more severe degree of scalp and body hair loss compared to TE.³⁰ Recently, etanercept and infliximab, 2 types of tumor necrosis factor-alfa inhibitors, have been associated with cases of new-onset LPP of the scalp.^{30,36} Therefore, a thorough drug history intake should be considered in every patient who presents with hair loss. Hair loss can occur days to months or even years after starting the offending medication. Exclusion of other causes of hair loss followed by identifying a compatible chronology of drug exposure and the onset of hair loss form the key to diagnose drug-induced alopecia.³⁰

NUTRITIONAL HISTORY

Key point

- Low protein and caloric intake can cause TE

Diet can be relevant to the condition of a patient's hair; ask particularly about protein intake. In strictly vegetarian patients, ask about nonanimal sources of protein. Hair fibers are composed primarily of keratin protein (98%).³⁷ Assess the patient's iron intake and ask about animal and nonanimal sources of iron. Metabolic and nutritional hypoproteinemia, low serum iron, crash diets, and sudden weight loss can all cause TE.^{38,39} Various eating disorders can also cause hair loss; according to 1 study,⁴⁰ TE occurred in 67% of patients with bulimia and in 61% of patients with anorexia nervosa.

PSYCHOSOCIAL HISTORY

Key point

- A variety of debilitating psychosocial disorders can cause hair loss

Psychiatric disturbances, such as acute anxiety and endogenous depression, have been considered possible causes of diffuse hair shedding.³ In addition, TE can result from severe stressful life events, such as financial bankruptcy, the end of a relationship, or the loss of a family member.⁴¹ The role of various stressful life events in the pathogenesis of AA has been controversial.⁴²⁻⁴⁴ On the other hand, adult-onset trichotillomania may be associated with an underlying psychiatric disease, and the assessment of the overall psychiatric health and psychosocial stressors is paramount in trichotillomania that develops in patients who are in the preschool or preadolescent age groups.⁵

HISTORY OF HAIR CARE PRACTICES AND THE USE OF HAIR COSMETICS

Key points

- Hair shafts can be adversely affected by various physical and chemical hair care practices
- CCCA has been linked to the overuse of chemical relaxers

Various physical and chemical factors can damage the hair shaft. Mechanical damage to the hair shaft can result from improper hair grooming. Frequent and prolonged contact with heat from a hair dryer can result in bubble hair.¹⁶ Ongoing and repeated tension on the hair during styling, such as wearing the hair back in a ponytail or using hair buns or turbans in Sikh men for a long time, can unintentionally lead to traction alopecia.⁶ Similarly, the overuse of chemical relaxers, permanent waves, hair dyes, or bleaching can result in significant hair shaft damage in some susceptible individuals.¹ The resulting hair can break easily and does not grow past a certain length. CCCA is a scarring alopecia that has been linked to the overuse of chemical relaxers¹⁰; this is more common in African American women.^{6,16}

FAMILY HISTORY

Key points

- A positive family history of the same hair condition can be seen in PHL, AA, and congenital hair shaft disorders
- A family history of other autoimmune diseases can be seen in patients with AA

A detailed family history of the same type of hair condition or any associated conditions should be

Table IV. Hair examination: Clinical checklist

Proper patient positioning

Overall scalp examination

Pattern

Distribution

Frontal hairline: integrity and density

Hair color

Hair length

Eyebrows and eyelashes

Close up examination

Scarring vs. nonscarring

Scalp epidermal changes

Erythema

Hypo-/hyperpigmentation

Scales/crusts

Papules/pustules

Hair tufting

Hair pull test

Hair card test

Tug test

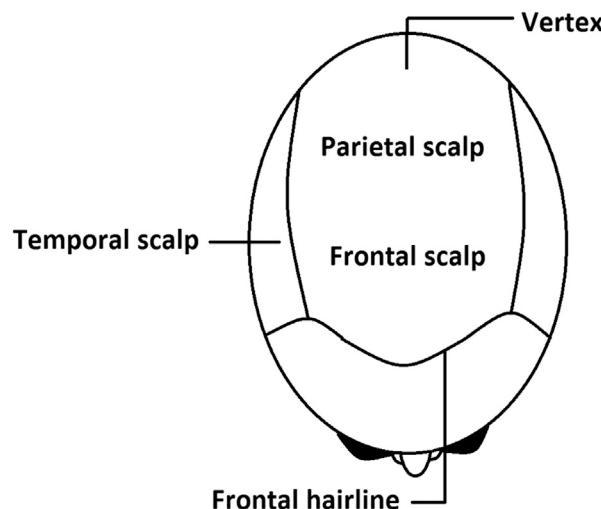


Fig 3. Anatomic regions of the scalp.

documented. In patients with PHL, ask about frontal scalp hair thinning in the patient's parents, grandparents, and siblings.^{9,14} A family history of AA or other autoimmune diseases, such as vitiligo, pernicious anemia, Hashimoto thyroiditis, and type I diabetes mellitus can be seen in patients with AA.^{4,23,45,46} In children with alopecia, a positive family history of a similar presentation points to the possibility of hereditary hair shaft disorders.^{16,17}

SPECIAL CONSIDERATIONS IN WOMEN: ANDROGEN EXCESS

Key point

- Alopecia in a pattern distribution can be seen in women with hyperandrogenism

In women, a detailed assessment of menstrual cycles, pregnancies, menopause, and the use of oral contraceptives or hormonal replacement therapies should be performed. Clinicians should assess the regularity of menstrual cycles and the heaviness of menstrual bleeding. Irregular cycles, infertility, hirsutism, persistent adult acne, and being overweight are symptoms of PCOS.⁴⁷ Patterned hair loss can occur in women with PCOS.^{14,47} Longer and heavier menstrual cycles can result in serum iron deficiency, which is a possible cause of TE.^{1,48,49} Postpartum TE usually occurs 2 to 3 months after childbirth and presents with excessive hair shedding.^{1,49} Older women should be evaluated for perimenopausal symptoms, such as hot flashes and irregular bleeding. In addition, starting or interrupting hormonal replacement therapies should be excluded as a possible cause of TE in this age group.^{1,8,30}

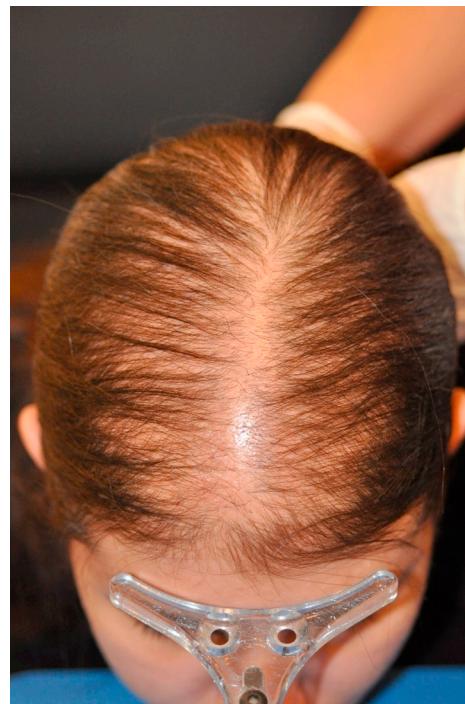


Fig 4. Female pattern hair loss. Note the marked thinning of hair on the frontal and the crown regions.

CLINICAL EXAMINATION

Key points

- A proper hair and scalp examination begins with positioning the patient on a chair and removing any hair pieces, extensions, or hair pins
- Full access to all portions of the scalp is crucial

For a proper scalp and hair examination, patients should be positioned on a chair rather than on an

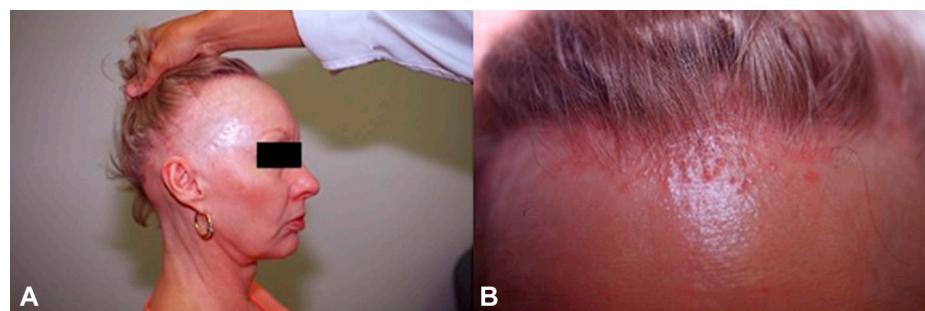


Fig 5. Frontal fibrosing alopecia. **A**, Prominent recession of the frontoparietal hairline. **B**, Perifollicular erythema with papules and lonely hair.

examination table. The patient's scalp must be examined 360°, including the back, front, top, and sides. In addition, a good lighting source and a magnifying lens or a dermatoscope should be available. Any hair pieces, extensions, or hair pins should be removed if possible (Table IV).

OVERALL SCALP EXAMINATION

Key points

- Recognizing the pattern and distribution of hair loss can help reach the correct diagnosis
- Scalp, facial, and body hair should all be assessed

First, clinicians should look at the patient's scalp hair from above; next, examine the sides and the back of the scalp. A visible scalp indicates a reduction of the hair density by at least 50% of normal.⁸ Visually compare the hair density over different parts of the scalp. Using your fingertips or the wooden end of a cotton swab, make serial sagittal parts of the hair starting from the frontal hairline to the crown and then from the occiput to the crown. Decide upon the pattern and the distribution of the hair loss. Certain alopecic patterns or distributions are commonly associated with certain diseases. A diffuse hair loss pattern may be seen in TE, such as drug-induced TE. A localized pattern confined to the frontal and the crown regions of the scalp is common in PHL. Hair thinning, which is mainly noted along the marginal hairline—frontally, temporally, and occipitally—is highly suggestive of traction alopecia.⁶ On the other hand, a randomly distributed and asymmetric pattern can be seen in AA, trichotillomania, or different types of scarring alopecia. Examine the frontal hairline. A subtle and receded hairline may be seen in PHL or FFA. More than 1 pattern of the hair loss can commonly coexist, which makes the assessment of the hair loss more difficult. TE can frequently unmask other types of alopecia, such as PHL. Note the color and the length

of the hair. Inspect the eyelashes, eyebrows, and facial hair (if any). Follow the same steps described previously. Both eyebrows and eyelashes can be involved in AA, FFA, or congenital hair shaft disorders.^{7,17,23} Examine the patient's face, and in women, note the presence of acne, hirsute hair growth, or follicular papules (Figs 3 and 4).

CLOSE-UP EXAMINATION: SCARRING VERSUS NONSCARRING

Key points

- Differentiate between scarring and nonscarring alopecia
- Redness, scales, dyspigmentation, atrophy, and the presence of telangiectasia should all be noted

The aim of this step is to differentiate between scarring and nonscarring alopecia. Take a closer look at the affected scalp using a magnifying lens or a dermatoscope. Check for the presence or absence of follicular ostia. Follicular markings are almost always absent in scarring alopecia.¹⁰ In nonscarring alopecia, follicular markings are usually present. Note scalp erythema, hypo- and hyperpigmentation, atrophy, perifollicular erythema, perifollicular scale, papules, pustules, crusting, telangiectasia, and hair tufting.^{1,8,20} Diffuse dryness and flaking of the scalp are the hallmark signs of seborrheic dermatitis.¹² Asymmetrical and well demarcated erythematous silvery scaly plaques are characteristic for scalp psoriasis¹¹ (Fig 5; Table V).

Assess the hair shaft. Examine the caliber, shape, and length. In addition, differentiate between a newly growing hair and broken hairs. To achieve the latter, use the hair card.

THE HAIR CARD

Key points

- The hair card is a simple examination technique that can be performed using a small

Table V. Scarring alopecia: Clinical features of the most common types

Characteristics	History	Clinical examination			
		Global appearance	Hair shedding	Pull test	Hair card
Lichen planopilaris	Age: adults Onset: gradual Scalp itching, burning sensation Lichen planus at other site in 50% of cases ²²	Bare patches or diffuse hair thinning Distribution: usually starts at parietal scalp plus perifollicular erythema or perifollicular scales	Variable	Positive: anagen hairs	No hair regrowth
Pseudopelade of Brocq	Age: young to middle age Onset: gradual No symptoms	Bare patches Distribution: mostly parietal scalp Irregular borders Hypopigmented and atrophic "footprints in the snow"	Variable	Positive: anagen hairs	No hair regrowth
Central centrifugal cicatricial alopecia	Age: young adults Onset: gradual and progressive Scalp itching, burning sensation with or without the role of hair care practices More in black females	Bare patch Distribution: starts on the crown and expands centrifugally Hair tufting can be present No signs of inflammation	Variable	Positive: anagen hairs	No hair regrowth
Discoid lupus erythematosus	Age: young adults Onset: gradual or abrupt Scalp itching, burning sensation More in white women SLE in 5-10% of cases ²⁰	Bare patches Distribution: parietal scalp Erythematous scaly papules, follicular plugging, hypopigmentation, peripheral hyperpigmentation, and telangiectasia	Variable	Positive: anagen hairs	No hair regrowth
Folliculitis decalvans	Age: young and middle age Onset: gradual Pain, scalp itching, burning sensation More in men	Bare patches Distribution: mostly starts at the vertex Follicular papules, pustules, and crusts Hair tufting	Variable	Positive: anagen hairs	No hair regrowth
Dissecting cellulitis	Age: young adults Onset: gradual Pain with or without follicular occlusion triad* More in men	Bare patches Distribution: mostly starts at the vertex boggy inflammatory plaques and nodules; with or without sinuses with purulent discharge	Variable	Positive: anagen hairs	No hair regrowth

SLE, Systemic lupus erythematosus.

*Follicular occlusion triad: hidradenitis suppurativa, acne conglobata, and dissecting cellulitis of the scalp.



Fig 6. The hair card showing short hairs with tapered ends.

white card for pigmented hair and a black card for white hair

- Newly growing hair can be easily differentiated from broken hair using the hair card

The hair card is an 8- × 12-cm piece of paper that is white on 1 side and black on the other.⁸ Both darker and lighter colored hairs easily contrast against the white and the black sides of the card, respectively. Place the card on the scalp and against the hair shafts in the affected area. Miniaturized hairs have smaller calibers than the surrounding hairs. Broken hairs have blunted ends, and newly regrowing hairs have pointed or tapered ends.^{16,17} Hair regrowth in affected sites is usually seen in nonscarring alopecia and may indicate a good response to therapy (Fig 6).

HAIR PULL TEST

Key point

- A positive hair pull test indicates active hair shedding and can be seen in TE and in active stages of AA or different scarring alopecias

The hair pull test is a simple diagnostic test that can be performed to determine the severity and the location of the hair loss. In the affected area, grasp 50 to 60 hairs between your thumb, index, and middle fingers. Pull firmly but gently away from the scalp and along the hair shafts. The test should be performed in 4 different regions of the scalp (ie, the frontal, occipital, and both temporal regions). The patient's hair should not be shampooed for at least 1 day. Normally, up to 10% of the scalp hair is in the telogen phase; being able to pull >5 or 6 hairs indicates ongoing hair loss activity, and is considered a positive pull test.^{1,8} In patients with AA, pull from both the center and the margins of the alopecic patch.^{4,8} A positive pull test yielding anagen hair bulbs is highly suspicious for primary scarring alopecia^{8,10,20} (Fig 7).



Fig 7. Demonstrating the hair pull test.



Fig 8. Demonstrating the tug test.

TUG TEST

Key point

- Hair shaft fragility can readily be detected using the tug test

The tug test is a simple clinical test that is used to show hair fiber fragility. With 1 hand, hold a group of hairs while your other hand pulls away the distal ends.⁸ Any hair breakage is considered abnormal and is a sign of hair fragility.⁸ The broken pieces of hair can then be used to prepare a hair mount (Fig 8).

HAIR MOUNT

Key point

- Microscopic examination of the hair bulbs and hair shafts can be easily performed to detect disorders of the hair cycle and to visualize structural hair shaft abnormalities

Hair mount is the classic method for assessing the hair bulbs and shafts using light microscopy. For the hair bulbs, epilated hair roots are placed on a glass slide. Then, a mounting medium should be added before arranging the hair roots side by side and covering the hair mount with a coverslip. Light microscopy is used to examine the hair mount. According to the stage of the hair cycle, different hair root types are then specified.⁵⁰ Anagen hair has a darkly pigmented bulb with a preserved inner root sheath. Telogen hair lacks the inner root sheath and

Table VI. Hair shaft disorders with increased fragility: Clinical features

Characteristics	History	Clinical examination		
		Global appearance	Tug test	Hair mount
Bubble hair	Acquired Age: young adults Overuse of blow dryer or curling irons Seen more often in women	Patchy, rarely generalized Short and kinky hair	Positive	Air bubble within hair shaft
Trichorrhexis nodosa	Acquired and congenital types exist Age: young adults Hair does not grow long Overuse of chemicals (ie, hair dyes and permanents) or repeated mechanical trauma (brushing) Seen more often in women	Patchy, rarely generalized Short and kinky hair with different lengths of hairs	Positive	Brush-like ends in opposition
Monilethrix	FHx in the congenital type Inheritance: AD or AR Age: children Hair breakage with varying degree of alopecia Keratosis pilaris in the occipital scalp, neck, and shoulder is the most common association May improve with puberty or pregnancy Inheritance: AR (Björnstad syndrome) or X-linked recessive (Menkes syndrome)	Patchy or generalized Short and kinky hair	Positive	Beaded nodes; wide segments (nodes) alternating with "internodes" constrictions
Pili torti	Age: children Hair does not grow long and breaks easily Bilateral deafness (Björnstad syndrome) Severe developmental and neurologic impairment (Menkes syndrome)	Patchy over pressure areas (eg, occipital and temporal areas) Short and shiny hair	Positive	Closely grouped twists
Trichorrhexis invaginata	Inheritance: AR Age: children Hair does not grow long Netherton syndrome: trichorrhexis invaginata, ichthyosis, and atopy	Patchy over pressure areas (eg, occipital and temporal areas) Short and kinky hair	Positive	Bamboo-like invaginations Can be seen easier in eyebrow hairs
Trichothiodystrophy	Inheritance: AR Age: children Brittle hair Associated with photosensitivity, ichthyosis, intellectual impairment, low fertility, and short stature	Patchy, rarely generalized Localized to areas of repeated trauma (eg, occipital and temporal areas) Short and kinky hair	Positive	Clean horizontal fractures (trichoschisis) Polarizing microscopy: alternating light and dark segments (tiger tail)

AD, Autosomal dominant; AR, autosomal recessive; FHx, family history.

Table VII. Hair shaft disorders with no hair fragility: Clinical features

Characteristics	History	Examination		
		Global appearance	Tug test	Hair mount
Woolly hair	Inheritance: inherited or sporadic Age: children Fine and tightly curled hair that is different from other family members Palmoplantar keratoderma, cardiofaciocutaneous syndrome, and Naxo disease are possible associations Cutaneous linear nevi can be associated with woolly nevus	Generalized: tightly curled hair Localized: woolly hairy nevus	Negative	No characteristic findings
Uncombable hair syndrome (pili trianguli et canaliculi)	Inheritance: AD or sporadic Age: children Unmanageable hair with difficulty in styling Hair grows normally long	Generalized Dry and silvery blond hair Hair appears to be standing away from scalp Normal hair density	Negative	Canal-like longitudinal groove along 1 or 2 facets of the hair shaft
Pili annulati	Inheritance: AD Age: children Shiny hair Hair grows normally long May be incidentally noted by a physician	Generalized Hair has bright and dark bands when viewed with a reflected light Normal hair density	Negative	Hair shaft has dark and light bands (dark bands correspond to abnormal air-filled cavities within the cortex)

AD, Autosomal dominant.

has a lightly pigmented to nonpigmented bulb with a distinctive club shape.^{8,50} Similarly, hair shafts can be examined to detect fractures, bubbles, irregularities, and twisting and to diagnose different hair shaft disorders, such as monilethrix, trichorrhexis invaginata, trichorrhexis nodosa, pili annulati, and pili torti.^{16,17,51} Trichoscopy has made hair mounts less necessary, because many hair shaft abnormalities can be evaluated with magnification several fold directly on the scalp (Tables VI and VII).

SCALP BIOPSY

Key point

- **Obtaining a skin biopsy specimen is the criterion standard tool for diagnosing scarring alopecia, and it is helpful for evaluating nonscarring alopecia**

Obtaining a skin biopsy specimen is considered the criterion standard tool for diagnosing different types of scarring alopecia.^{1,22} In addition, it can provide additional information in cases of unexplained nonscarring alopecia.^{1,8,52} All types of skin biopsy specimens can be obtained safely in patients who are undergoing warfarin, heparin, clopidogrel, or aspirin therapy if the biopsy site is planned carefully and appropriate hemostasis settings are

readily available.⁵³ Similarly, patients using nonsteroidal antiinflammatory drugs or a number of alternative therapies, such as garlic, ginger, fish oil, green tea, and ginkgo biloba—all of which can produce a prolonged bleeding time—can safely undergo a skin biopsy and other dermatologic procedures that generally have a low risk of bleeding.⁵⁴ Choose an active area of the scalp with persistent hair fibers (preferably cosmetically hidden). Avoid completely bald areas.⁵² Have the hair within the 4-mm biopsy site clipped to 1 to 2 mm in length. Inject 0.1 mL of 1% lidocaine and epinephrine (1:100,000) into the scalp and wait for 10 minutes for maximum hemostasis. Take 1 to 2 biopsy specimens from the periphery of the affected area. The biopsy specimen should follow the direction of the hair growth and reach deeply into the subcutaneous tissue where the bulbs of scalp anagen hair follicles usually reside.^{1,52} Using a blue monofilament suture, close the biopsy site. Whereas hematoxylin–eosin horizontal sectioning allows a large number of hair follicles to be studied under the microscope, a vertical section provides more information on the entire length of the hair follicle.⁵⁵ Therefore, horizontal sectioning may be more suitable for suspected nonscarring alopecia, and either horizontal or vertical sectioning can be requested for suspected scarring alopecia with the

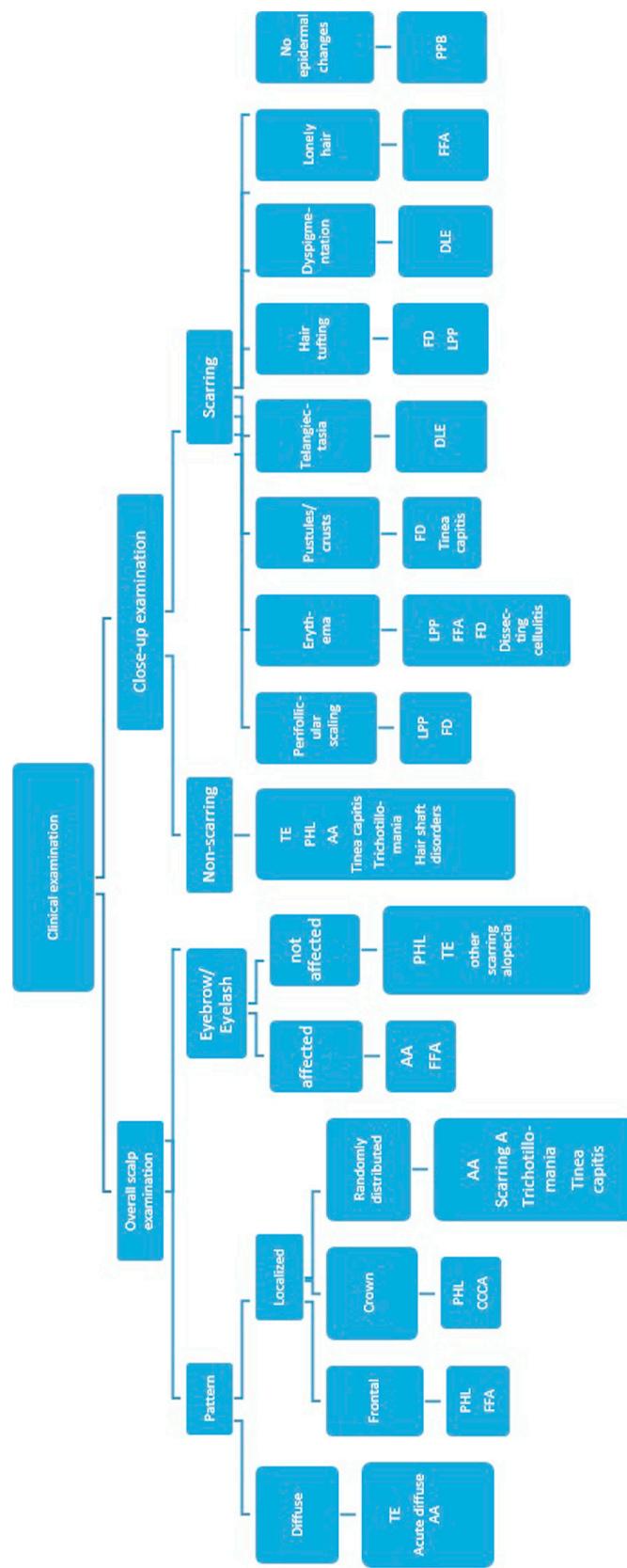


Fig 9. Hair and scalp examination: algorithmic approach. *A*, Alopecia; *AA*, alopecia areata; *CCCA*, central centrifugal cicatricial alopecia; *scarring DLE*, discoid lupus erythematosus; *FD*, folliculitis decalvans; *FFA*, frontal fibrosing alopecia; *LPP*, lichen planopilaris; *PHL*, patterned hair loss; *PPB*, pseudopelade of Brocq; *TE*, telogen effluvium.

exception of LPP. For the latter, vertical sectioning may be more informative.^{55,56} Half of 1 biopsy specimen or another 2-mm punch biopsy specimen can be sent for direct immunofluorescence in some cases of scarring alopecia, such as DLE⁵⁶ (Fig 9).

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Evaluation and diagnosis of the hair loss patient

Part II. Trichoscopic and laboratory evaluations

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Learning Objectives

After completing this learning activity, participants should be able to describe how to perform trichoscopy and interpret relevant laboratory investigations for the diagnosis of hair disorders.

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The use of trichoscopy for evaluating a number of hair and scalp disorders is gaining popularity. It is a simple and noninvasive *in vivo* tool for visualizing hair shafts and the scalp. Recently, alopecias have been classified according to their trichoscopic findings. The second part of this 2-part continuing medical education article reviews recent advances in this field and describes a systematic approach for using the differential diagnostic findings of trichoscopy in alopecia. (*J Am Acad Dermatol* 2014;71:431.e1-11.)

Key words: alopecia areata; androgenetic alopecia; dermatoscopy; dermoscopy; discoid lupus erythematosus; dissecting cellulitis; lichen planopilaris; patterned hair loss; trichoscopy; videodermatoscopy.

TRICHOSCOPY

Trichoscopy is dermatoscopy of the hair and scalp.¹ This is a noninvasive, in-office technique that can be performed with a handheld dermatoscope or a digital videodermatoscopy system.² Trichoscopy allows for magnified observation of the following: (1) hair shafts, (2) hair follicle openings, (3) the perifollicular epidermis, and (4) blood vessels. Abnormalities in the appearance of these 4 structural components of the scalp aid in the differential diagnosis of hair loss.^{3,4}

Equipment

Key points

- Trichoscopy is based on hair and scalp evaluation by an expert dermatologist
- For some applications, software is available to aid expert evaluation

Any handheld dermatoscope or videodermatoscope (digital dermatoscope) may be used to perform trichoscopy (Fig 1).⁵ Most handheld dermatoscopes allow for observation of the skin surface at 10-fold magnification, while digital dermatoscopes have working magnifications ranging from 10- to 50-fold and higher.^{3,4} Handheld dermatoscopes have the advantage of being both time- and cost-effective, while digital dermatoscopes allow for easier

CAPSULE SUMMARY

- Any dermatoscope (handheld or digital) may be used to perform trichoscopy.
- Trichoscopy is a quick, noninvasive, cost effective, bedside technique that provides key physical diagnostic information to assist in the accurate diagnosis of alopecia.

photography and higher working magnifications. The choice of a particular device is a matter of individual preference.^{3,4}

Some digital videodermatoscopes are multitask devices, while others—such as the Follicope (LeadM Corporation, Seoul, Korea)—are primarily intended for hair evaluation. The Follicope is an USB connection-based device that is equipped with software that allows the assessment of hair shaft thickness using trichoscopy images.⁶

The Trichoscan (Tricholog GmbH, Freiburg, Germany) was developed to analyze hair growth in consecutive trichoscopy images. Although the Trichoscan has found support among many dermatologists,⁷ it has been criticized by others for its requirement to shave and dye hair in the analyzed area.^{8,9}

TRICHOSCOPY STRUCTURES AND PATTERNS

Hair shafts

Key point

- Structural abnormalities of the hair shaft may provide diagnostic clues for multiple causes of hair loss beyond genetic hair shaft defects

A normal terminal hair is uniform in thickness and color throughout its length.^{10,11} However, up to 10%

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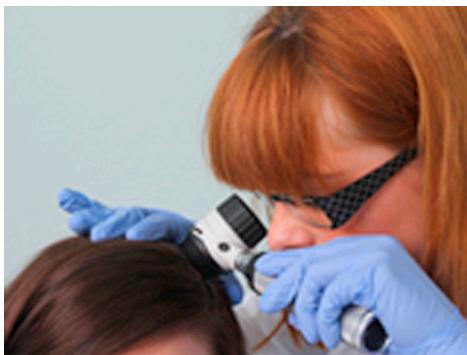


Fig 1. Any dermatoscope (handheld or digital) may be used to perform trichoscopy.

of normal human scalp hairs are vellus hairs^{10,11} that are lightly pigmented and measure <3 mm in length and <30 µm in thickness. An increased proportion of vellus hairs may be present in patterned hair loss (PHL) and in long-lasting alopecia areata (AA). Vellus hairs can be differentiated from short, healthy regrowing hairs, which are darkly pigmented and straight with pointed ends. Abnormalities in hair shaft structure may provide diagnostic clues for multiple acquired and inherited causes of hair loss.¹² Such abnormalities include exclamation mark hairs (in AA, trichotillomania, and chemotherapy-induced alopecia), Pohl–Pinkus constrictions (in AA, chemotherapy-induced alopecia, blood loss, malnutrition, and chronic intoxication), comma hairs (tinea capitis), corkscrew hairs (tinea capitis), coiled hairs (trichotillomania), flame hairs (trichotillomania), and tulip hairs (trichotillomania and AA; Fig 2). Trichoscopy has also been successfully used to diagnose many genetic hair shaft disorders.¹³ Rudnicka et al¹² recently proposed a classification of hair shaft abnormalities observed by trichoscopy (Table I).

Hair follicle openings: Dots

Key point

- **Hair follicle openings appear in trichoscopy as small round structures, called “dots”**

The term “dots” refers to the small, round hair follicle openings seen on trichoscopy (Fig 3).¹⁴

Black dots are residues of pigmented hairs that have been broken or destroyed at the level of the scalp.¹⁵ They are observed in >40% of patients with AA and are considered a marker of high disease activity.¹⁶ Black dots may be present in dissecting cellulitis, tinea capitis, chemotherapy-induced alopecia, trichotillomania, and as incidental findings in other diseases.^{15,17} Black dots are not present in healthy individuals or in patients with PHL or telogen effluvium (TE).^{10,18}

Yellow dots are follicular openings filled with keratotic material and/or sebum.^{14,19} Regularly

distributed yellow dots are present in >60% of patients with AA and are considered a marker of disease severity and less favorable prognosis.¹⁶ Large, dark yellow to brownish-yellow dots (keratotic plugs) are characteristic of discoid lupus erythematosus (DLE) and correspond to wide infundibula filled with keratotic material.^{20,21} Yellow dots are also seen in patients with PHL.¹⁸ They differ from the yellow dots observed in other diseases by their “oily” appearance that most probably results from the predominance of sebum over keratotic material.⁴ Yellow dots imposed over dark hair shaft residues have been described in dissecting cellulitis²⁰ and in trichotillomania.¹⁶

White dots may appear as fibrotic white dots or pinpoint white dots. The fibrotic white dots are small, irregular areas of fibrosis, observed in primary, folliculocentric cicatricial alopecias, and most commonly in lichen planopilaris (LPP).^{14,20} The pinpoint white dots are small and regular, with occasional peripheral hyperpigmentation. They are observed on dark skin in healthy individuals and patients with noncicatricial alopecia.^{22,23} Pinpoint white dots correspond to empty hair follicle openings and eccrine sweat gland ducts that appear whitish on the contrasting, pigmented background.²⁴

Red dots have been described in DLE²⁵ and in individuals with vitiligo.²⁶ Pink-grey and grey dots have been observed in the eyebrow area of patients with frontal fibrosing alopecia (FFA).⁴

Peri- and interfollicular areas

Key point

- **The color and structure of peri- and interfollicular areas may provide important diagnostic clues**

The classification of peri- and interfollicular skin surface abnormalities in trichoscopy is based on features related to scaling, color, discharge, and surface structure.³

Epidermal scaling is a common finding in healthy individuals and in various inflammatory scalp diseases. Mild, diffuse scaling may be an incidental finding or may be associated with use of topical gels or alcohol-based solutions. Intense, diffuse scaling is commonly associated with inflammatory scalp diseases (eg, psoriasis and seborrheic dermatitis). Perifollicular scaling with the formation of tubular scaly structures around hair shafts is observed in LPP and in folliculitis decalvans.^{2,20} In addition, diffuse scaling with formation of white perifollicular clusters requires differential diagnosis with the follicular spicules observed in monoclonal gammopathy of undetermined significance.⁴

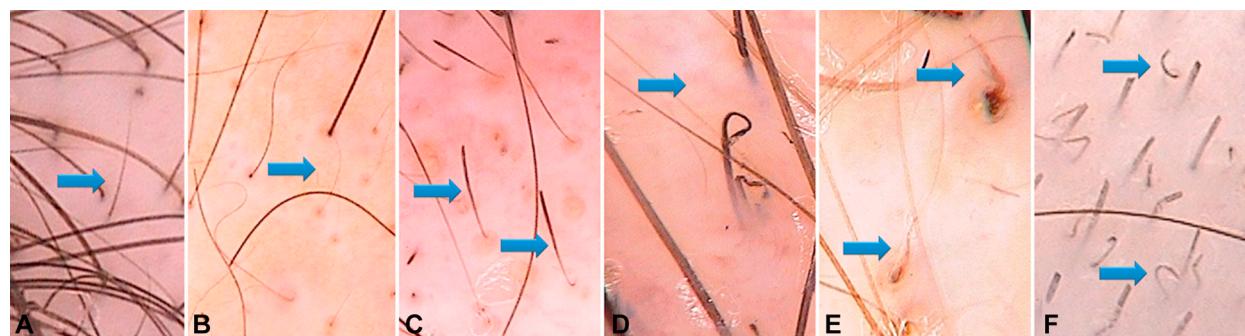


Fig 2. Common types of hair shafts in trichoscopy. **A**, Upright regrowing hairs. **B**, Vellus hairs. **C**, Exclamation mark hairs. **D**, Coiled hairs. **E**, Flame hairs. **F**, Comma hairs. (Original magnification: $\times 50$.)

Hyperpigmentation of the scalp may appear in 3 different distribution patterns: honeycomb, perifollicular, and scattered interfollicular.^{1,27} Honeycomb hyperpigmentation¹⁴ is a normal finding in sun-exposed areas and in patients with Fitzpatrick skin phototypes IV, V, and VI.^{2,28} Perifollicular brown coloration ("peripilar sign") is believed to correspond to the perifollicular presence of lymphocytic infiltrates²⁹ and is common in patients with PHL.³⁰ However, the peripilar sign may be observed in up to 10% of hair follicles in healthy individuals.¹⁰ Scattered brown discoloration is characteristic of DLE.²⁰

Other common trichoscopy signs include yellow or yellow-red discharge (eg, folliculitis decalvans, bacterial infections, dissecting cellulitis, and tinea capitis) and structural changes in the skin surface (eg, starburst pattern hyperplasia in folliculitis decalvans).^{4,20}

Blood vessels

Key point

- Several inflammatory scalp disorders are characterized by a specific pattern of blood vessel arrangement on trichoscopy

The significance of blood vessel abnormalities observed on trichoscopy has not been explored in detail thus far. A recent classification⁴ distinguishes¹⁸ types of vessels, including elongated vessels (in LPP), thick arborizing vessels (DLE), and glomerular or coiled vessels in linear or circular alignment (psoriasis).^{20,31}

DISTINGUISHING NONCICATRICIAL FROM CICATRICIAL ALOPECIA USING TRICHOSCOPY

Key point

- The presence of hair follicle openings differentiates noncicatricial from cicatricial alopecia

The identification of noncicatricial alopecia is primarily based on the presence of follicular

openings, manifesting in trichoscopy as empty, yellow, or black dots.¹⁴ However, dots may not be visible in some cases of noncicatricial alopecia, especially in psoriatic alopecia,⁴ childhood AA, or long-lasting AA.^{4,28} In long-lasting AA, yellow dots may reappear after corticosteroid treatment.³²

However, the presence of follicular openings is not an absolute sign for diagnosing noncicatricial alopecia. Follicular openings may be visible in the early, noncicatricial phases of DLE^{21,25} and dissecting cellulitis.^{20,33}

The absence of dots and the concomitant presence of milky red areas is typical of recent onset fibrosis,⁴ and these features allow greater certainty in the diagnosis of cicatricial alopecia than the sole absence of dots (Fig 4).

ACQUIRED NONCICATRICIAL ALOPECIA

Alopecia areata

Key points

- Trichoscopy of AA most commonly shows yellow dots, black dots, and exclamation mark hairs
- Trichoscopy enables the assessment of disease activity in AA

Trichoscopic findings associated with AA have been investigated in detail by many authors.^{5,14,16,22,34-36} The most characteristic trichoscopic features of AA are yellow dots (63-94% of patients), black dots (44-70%), exclamation mark hairs (30-44%), tapered hairs (12-42%), broken hairs (45-58%), vellus hairs (33-72%), trichorrhexis nodosa (3-16%), monilethrix-like hairs (2-3%), and Pohl-Pinkus constrictions (<3%).⁴

Active (acute) AA can be distinguished from nonactive AA using trichoscopy. Features of disease activity include black dots, exclamation marks, and broken hairs, whereas yellow dots and vellus hairs are markers of disease severity and inactive late-stage disease (Fig 5).^{16,19,34}

Table I. Trichoscopic findings in genetic hair shaft disorders

Disorder	Trichoscopic findings
Hair shaft disorders with increased fragility	
Monilethrix	Uniform elliptical nodosities and intermittent constrictions causing regular variations in hair shaft thickness, hairs bend and break at constriction sites, and whitish or yellowish keratotic follicular plugs
Pili torti	Twists of hair shafts along their long axis; best visible with dry trichoscopy
Trichorrhexis invaginata	Multiple small nodules spaced along the shaft (handheld dermatoscope); invagination of the distal portion of the hair shaft into its proximal portion forming a "ball in cup" appearance (digital dermatoscope); and golf tee-like hairs (distal ends of a broken hairs)
Trichorrhexis nodosa	Nodular thickening along hair shafts (handheld dermatoscope); numerous small fibers, which produce a picture resembling 2 brushes aligned in opposition (digital dermatoscope); best visible with dry trichoscopy
Trichothiodystrophy	Trichoscopy is noncharacteristic, may be suspected based on trichoschisis (a clean transverse fracture across the hair shaft) and a slightly wavy contour of hair shafts
Hair shaft disorders without increased fragility	
Pili annulati	Subtle, cloudy white, transverse bands in the hair shafts
Woolly hair	Hair shafts with waves at very short intervals ("crawling snake" appearance); trichoscopy is not very helpful for diagnosis
Loose anagen hair syndrome	No hair shaft abnormalities in trichoscopy
Short anagen hair syndrome	No hair shaft abnormalities in trichoscopy

Early features of hair regrowth include the presence of pigmented, upright, regrowing hairs¹⁶ and pigtail hairs.²⁷ Recent data show that trichoscopy may also be applied in the evaluation of treatment response in AA patients.^{37,38}

PATTERNEDE HAIR LOSS

Key points

- Hair shaft thickness heterogeneity is the most prominent trichoscopic feature of PHL
- In patients with PHL, trichoscopic abnormalities are more pronounced in the frontal area compared with the occipital area

Male pattern hair loss (MPHL) and female pattern hair loss (FPHL) share similar trichoscopic features. These include hair shaft thickness heterogeneity (ie, the simultaneous presence of thin, intermediate, and thick hairs), yellow dots, perifollicular discoloration (peripilar sign), an increased proportion of vellus hairs, and an increased proportion of follicular units with only 1 emerging hair shaft (Fig 6).^{14,18,19,39}

The presence of yellow dots appears to be a variable feature of PHL. In various studies, yellow dots have been observed in 66%,¹⁸ 30.5%,⁵ 10% to 26%,³⁹ and 7%¹⁴ of patients with PHL, while brown perifollicular discoloration (peripilar sign) has been observed in 20% to 66% of patients.^{18,39}

All of the trichoscopic features of PHL appear most prominently in the frontal scalp area.^{10,18}

TELOGEN EFFLUVIUM

Key points

- Trichoscopy is not diagnostic for TE
- Multiple short upright regrowing hairs may indicate the regrowth phase of TE

Trichoscopy appears to have limited diagnostic value for TE. Frequent—but not specific—trichoscopic findings for TE include empty hair follicles, a high percentage of follicular units with only 1 hair, and brown perifollicular discoloration (the peripilar sign). Multiple upright regrowing hairs may be observed in the regrowth phase of TE (Fig 7).^{18,40}

In TE patients, no significant differences are observed in the trichoscopic findings between the frontal and occipital areas; this differentiates TE from PHL. However, clinicians should be aware about the frequent coexistence of these 2 conditions.⁴

TRICHOTILLOMANIA

Key point

- Chaotic arrangement of multiple broken hair shafts is a key feature of trichotillomania

The usual trichoscopic finding in trichotillomania is the simultaneous, chaotic coexistence of multiple hair shaft abnormalities with no significant changes in the perifollicular area (Fig 8).

Hair shaft abnormalities in trichotillomania include hairs broken at different lengths, short hairs with trichoptilosis (ie, split ends), coiled hairs,

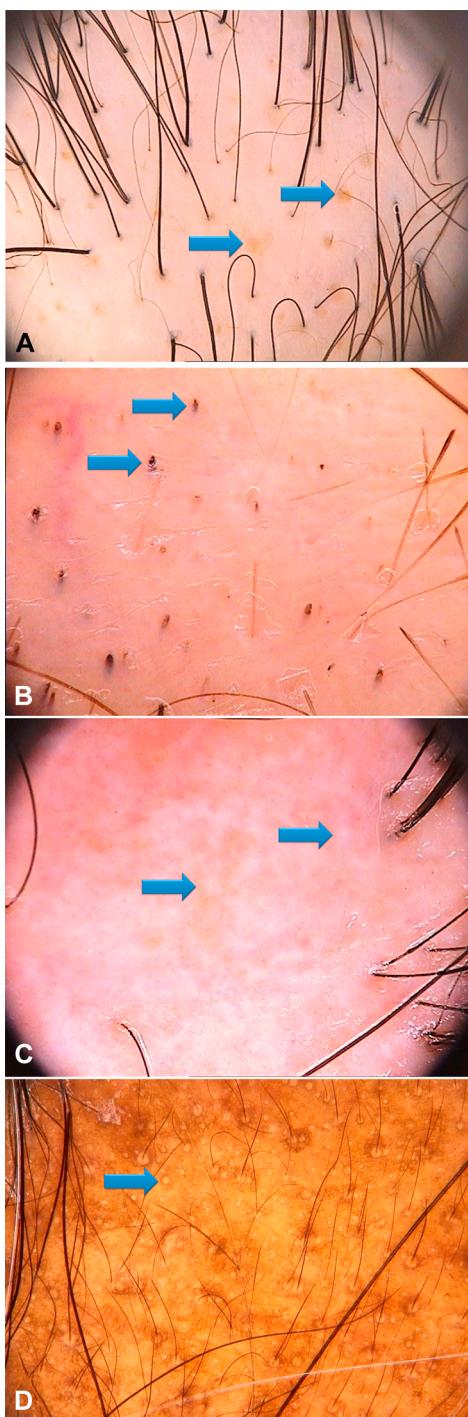


Fig 3. Dots in trichoscopy. **A**, Yellow dots in female pattern hair loss. **B**, Black dots in alopecia areata. **C**, Fibrotic white dots in lichen planopilaris. **D**, Pinpoint white dots seen on the normal scalp of a person with a dark skin phototype. (Original magnification: $\times 20$.)

exclamation mark hairs, and hair shaft residues (ie, black dots).^{14,36,41} Yellow dots are generally not observed in trichotillomania.³⁶ Sparse yellow dots with black hair residues in their central part may be seen.^{16,42}



Fig 4. An area lacking follicular openings in a patient with cicatricial alopecia. The milky-red (strawberry ice cream) color is indicative of fibrosis of recent onset. (Original magnification: $\times 20$.)

Recently, new characteristic trichoscopic features of trichotillomania have been described, including flame hairs, the V-sign, hook hairs, hair powder, and tulip hairs.⁴³ Flame hairs (Fig 2, E) are seen in 25% of patients with trichotillomania and are highly specific for the condition. They are semitransparent, wavy, cone-shaped hair residues that remain attached to the scalp after anagen hairs have been pulled out. A V-sign is created when ≥ 2 hairs emerging from 1 follicular unit are pulled simultaneously and break at the same length above the scalp surface. Tulip hairs are short hairs with darker, tulip flower-shaped ends. It has been hypothesized that these are diagonally fractured hair shafts.⁴³ In trichotillomania, hair shafts may be totally damaged by mechanical manipulation, so that only sprinkled hair residues ("hair powder") remains visible.⁴³

TINEA CAPITIS

Key point

- **Comma hairs and corkscrew hairs are hallmark trichoscopic features of tinea capitis**

The potential usefulness of trichoscopy as a supplementary method in the differential diagnosis of tinea capitis was first documented by Slowinska et al⁴⁴ who described characteristic comma hairs (Fig 2, F) in a *Microsporum canis* infection. Subsequent reports noted that comma hairs are associated with both ectothrix and endothrix types of fungal invasion.⁴⁵⁻⁴⁷

In some patients, hairs are more intensely coiled than typical comma hairs. These hairs have been called "corkscrew hairs."^{44,46,47} Other less common findings include Morse code hairs² and black dots.⁴³

Ultraviolet-enhanced trichoscopy is a new, trichoscopy-based method that may aid in the identification of tinea capitis. In this method, trichoscopy is performed along with a Wood's light, which

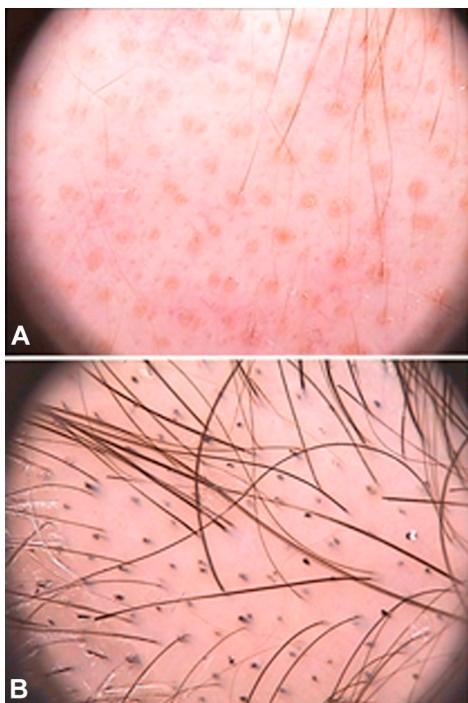


Fig 5. Trichoscopy allows for the assessment of disease activity in alopecia areata. **A**, The presence of regularly distributed yellow dots and vellus hairs is indicative of severe, long-lasting alopecia areata and low disease activity. **B**, Multiple black dots and exclamation mark hairs are markers of high disease activity. (Original magnification: $\times 20$.)



Fig 6. Trichoscopy of patterned hair loss reveals hair shaft thickness heterogeneity, multiple vellus hairs, and a predominance of follicular units with only 1 hair. (Original magnification: $\times 20$.)

allows the physician to observe the characteristic fluorescence in individual hair shafts.²⁷

ANAGEN EFFLUVIUM

Key point

- Chemotherapy-induced alopecia is characterized by presence of black dots, monilethrix-like hairs, and exclamation mark hairs

Anagen effluvium is a common term for multiple conditions with diverse trichoscopic features.



Fig 7. Trichoscopy revealing the regrowth phase of telogen effluvium with multiple upright regrowing hairs. (Original magnification: $\times 20$.)



Fig 8. Trichoscopy images of trichotillomania may vary depending on the frequency, intensity, and technique of hair pulling. The most consistent finding is the presence of multiple broken hairs that differ in length and shape. In the upper part of the image, a hook hair (a partly coiled hair shaft) is visible. (Original magnification: $\times 20$.)

Trichoscopic images of anagen effluvium induced by toxic factors (eg, chemotherapy-induced alopecia) are characterized by the presence of black dots, monilethrix-like hairs, and exclamation mark hairs.^{15,17}

In loose anagen syndrome, trichoscopic findings are not specific, revealing sparse hairs, a decreased number of hair shafts per follicular unit and, occasionally, trichorrhesis nodosa.⁴

In short anagen syndrome, trichoscopy reveals normal hair density and numerous, short, regrowing hairs of different lengths.^{4,48}

PRIMARY CICATRICIAL ALOPECIA

Lichen planopilaris

Key point

- Intense perifollicular scaling is the most characteristic trichoscopic feature of LPP

The most characteristic feature of active LPP is perifollicular scaling.^{49,50} Scales migrate along the



Fig 9. Trichoscopy of lichen planopilaris reveals perifollicular scaling. Scales migrate along the hair shafts and form tubular structures that cover the proximal portion of the emerging hair shaft (tubular perifollicular scaling). (Original magnification: $\times 20$.)

hair shafts and form tubular structures that cover the proximal portions of the emerging hair shafts (Fig 9). This phenomenon is called “tubular perifollicular scaling.”²⁰ The hair shaft may be covered by scales up to a few millimeters above the scalp surface. This feature is best observed with dry trichoscopy.

Other trichoscopic features of active LPP include the presence of elongated linear blood vessels in concentric arrangement and violaceous inter- or perifollicular violaceous areas and are more prominent in patients with dark phototypes.⁵¹

Trichoscopy of inactive end-stage LPP reveals small, irregularly shaped, whitish areas lacking follicular openings, called “fibrotic white dots,” and white areas of conducted fibrosis.^{14,20,51} Milky-red areas are characteristic for inflammation-mediated fibrosis of recent onset.²⁰ Small hair tufts, of 5 to 9 hairs, may be present in late LPP.²⁰

Frontal fibrosing alopecia

Key point

- The most common trichoscopic findings in FFA include the lack of follicular openings and minor perifollicular scaling

FFA is a condition within the spectrum of LPP⁵²⁻⁵⁴; both of these diseases share some trichoscopic features.²⁰ Trichoscopic findings in FFA include the lack of follicular openings and minor perifollicular scaling.⁵²⁻⁵⁵ On occasion, perifollicular erythema may be observed. There is a strong predominance of follicular openings with only 1 hair at the hair-bearing margin.²⁰ Lonely hairs, surrounded by areas of fibrosis,⁵² and the absence of vellus hairs in the frontal hairline⁵³ have been discussed as possible clues for the diagnosis of FFA. Arborizing vessels have been described in 1 study⁵¹; however, this has not been confirmed by other authors.^{54,55} The



Fig 10. Discoid lupus erythematosus. Large yellow dots (follicular keratotic plugs) are characteristic. (Original magnification: $\times 20$.)

background in patients with FFA is usually ivory-white to ivory-beige.^{54,55}

Pink-grey and grey dots are commonly observed in the lateral eyebrow area of patients with FFA.^{4,27}

Folliculitis decalvans

Key point

- Hair tufts that contain 5 to >20 hairs are the most characteristic trichoscopic finding in folliculitis decalvans

The most characteristic trichoscopic feature of folliculitis decalvans is the presence of hair tufts that contain 5 to >20 hair shafts.⁵⁶ At the base, these hair tufts are commonly surrounded by a band of yellowish scales (yellowish tubular scaling)²⁰ and by perifollicular epidermal hyperplasia, which may be arranged in a starburst pattern.²⁰ Other trichoscopic findings in active folliculitis decalvans include follicular pustules and yellow discharge.⁴ A perifollicular concentration of blood vessels may also be present.²⁰ In long-standing disease, white and milky-red areas lacking follicular openings are predominant. Folds of epidermal hyperplasia may also be present.^{20,57}

Dissecting cellulitis (perifolliculitis capitis abscedens et suffodiens)

Key points

- Early dissecting cellulitis may mimic non-cicatricial alopecia
- Trichoscopic findings in advanced dissecting cellulitis include yellow structureless areas and 3-dimensional yellow dots imposed over dystrophic hair shafts

Early dissecting cellulitis is characterized by the presence of empty follicular openings, yellow dots, and black dots and may mimic AA.^{15,33} As the disease progresses, other trichoscopic features become more

prominent, including yellow structureless areas and yellow dots with “3-dimensional” structure imposed over dystrophic hair shafts.²⁰ End-stage fibrotic lesions are characterized by confluent ivory-white or white areas lacking follicular openings.^{20,58}

Discoid lupus erythematosus

Key points

- Trichoscopy of DLE is characterized by large yellow dots, occasionally with superimposed thin blood vessels (“red spiders in yellow dots”)
- Thick arborizing vessels may be present at the periphery of lesions

One of the most typical trichoscopic features of active DLE is the presence of large yellow dots (follicular keratotic plugs).^{20,21,51} These dots differ from the yellow dots observed in AA by their larger size and darker, yellow-brownish color (Fig 10). Occasionally, in long-lasting DLE, thin and radial arborizing vessels are observed to emerge from these dots (“red spider in yellow dot” appearance). Thick arborizing vessels are commonly present at the periphery of the lesion.²⁰ Follicular red dots may occasionally be present and are considered a good prognostic factor of hair regrowth.^{20,25}

Trichoscopic findings for long-lasting, inactive DLE lesions do not differ from those for other types of cicatricial alopecia and are characterized by structureless milky-red or white areas lacking follicular openings.²⁰

GENETIC HAIR SHAFT DEFECTS

Key point

- All genetic hair shaft defects except trichothiodystrophy may be diagnosed by trichoscopy

Trichoscopy may replace light microscopy in the evaluation of genetic hair shaft defects, such as monilethrix,^{59,60} trichorrhexis invaginata,^{61,62} trichorrhexis nodosa,¹³ pili annulati,^{13,63} pili torti,^{14,63} and others.⁶⁴ The advantage of trichoscopy is that it allows a general inspection of all scalp hairs to find the hair shafts with the structural defect(s). When using light microscopy, multiple samples may be needed before an abnormal hair shaft is identified.

In trichothiodystrophy, the characteristic tiger tail pattern is not visible on trichoscopy, and polarized microscopy remains the criterion standard for diagnosing this condition.^{13,42}

Trichoscopy-guided biopsy

Trichoscopy may serve as an independent diagnostic method; however, it may also be used to

identify the best area from which to obtain a biopsy specimen. Trichoscopy-guided biopsy can rapidly identify individually affected follicles and allow accurate pathologic assessment.⁶⁵

The laboratory evaluation of patients presenting with various types of alopecia has been extensively discussed in other review articles, and the reader is invited to refer to some of these articles.^{66,67}

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Screening, early detection, education, and trends for melanoma: Current status (2007-2013) and future directions

Part I. Epidemiology, high-risk groups, clinical strategies, and diagnostic technology

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After completing this learning activity, participants should be able to describe current trends in melanoma incidence/mortality, risk factors for melanoma severity, and the tools for determining each patient's risk of melanoma.

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While most cancers have shown both decreased incidence and mortality over the past several decades, the incidence of melanoma has continued to grow, and mortality has only recently stabilized in the United States and in many other countries. Certain populations, such as men >60 years of age and lower socioeconomic status groups, face a greater burden from disease. For any given stage and across all ages, men have shown worse melanoma survival than women, and low socioeconomic status groups have increased levels of mortality. Novel risk factors can help identify populations at greatest risk for melanoma and can aid in targeted early detection. Risk assessment tools have been created to identify high-risk patients based on various factors, and these tools can reduce the number of patients needed to screen for melanoma detection. Diagnostic techniques, such as dermatoscopy and total body photography, and new technologies, such as multispectral imaging, may increase the accuracy and reliability of early melanoma detection. (J Am Acad Dermatol 2014;71:599.e1-12.)

Since the most recent review article (2007) regarding the screening and early detection of melanoma,¹ there have been numerous studies of significance to dermatology, clinical medicine, and public health. In particular, screening and education studies in the United States and Germany have been strongly associated with reductions in melanoma mortality. These findings are significant, because melanoma remains the only preventable cancer for which the mortality rate has not declined.

In part I of this continuing medical education article, we highlight updates in melanoma epidemiology, the identification of high-risk groups, clinical strategies for earlier detection, and novel diagnostic technologies. Part II focuses on the latest international and domestic data regarding the efficacy of skin screening, implications for a potential US melanoma screening initiative, the need for increased public and health professional education efforts, and future directions to enhance early melanoma detection.

We reviewed PubMed, Embase, CINAHL, and Cochrane databases using the following search terms: melanoma, incidence, mortality, early detection, screening, thickness, race, dermatoscopy/dermatoscopy, education, population-based, self-examination, and skin examination. We identified additional studies by reviewing the reference lists of all studies included herein. Every effort was made to use only the most recently published studies (ie, 2007-2013); in a few cases, key studies before 2007 were included. In some cases, actual studies were conducted before 2007 but reported in the period between 2007 and 2013.

Abbreviations used:

CSLM:	confocal scanning laser microscopy
MC1R:	melanocortin-1 receptor
PD:	Parkinson disease
SEER:	Surveillance Epidemiology and End Results
SES:	socioeconomic status

INCIDENCE AND MORTALITY TRENDS IN THE UNITED STATES AND INTERNATIONALLY

Key points

- In the United States, incidence rates of melanoma have continued to increase while mortality rates have only recently stabilized
- The steepest rise in incidence rates has been in men >60 years of age and in lower socioeconomic areas
- For any given stage and across all ages, men have poorer melanoma survival than women
- Internationally, various countries have seen similar increases in melanoma incidence and mortality

Incidence

The incidence of melanoma is increasing at a faster rate than any other preventable cancer in the United States.² According to data from the Connecticut Tumor Registry between 1950 and 2007, incidence rates rose more than 17-fold in men (1.9 to 33.5 per 100,000) and more than 9-fold in women (2.6 to 25.3 per 100,000).³ The latest projections predict that there will be >76,000

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invasive melanomas diagnosed in the United States in 2014 and >9000 people will lose their lives to this disease.⁴ Between 1992 and 2004, incidence annually increased by about 3.1%.⁵

The previous review discussed rising incidence rates of melanoma for older men, and this trend has worsened for the 25-year period from 1983 to 2007, during which men aged 60 to 64 years experienced a 2-fold increase in incidence, whereas men aged 75 to 79 years had a 4-fold increase.⁶ Between 1992 and 2004, the incidence of melanoma increased for tumors of all histologic subtypes and thicknesses. While this increase may be attributed to higher rates of melanoma screening, the sharpest increase in incidence was evident among low socioeconomic status (SES) areas, where individuals are least likely to undergo screening, suggesting that increasing incidence rates are not simply an artifact of screening.⁵

Black patients have a lower incidence of melanoma than whites, but the 5-year relative survival for blacks with melanoma is 74.1% compared with 92.9% for whites. Moreover, the majority of melanomas in black patients are on nonexposed skin areas, such as the lower limb, hip, and trunk. These atypical locations may contribute to the lower survival for black patients.⁷ For Hispanic patients, data from the California Cancer Registry between 1988 and 2001 showed that there was a 1.8% per year increase in incidence of invasive melanomas, and there was a disproportionate increase in the number of tumors thicker than 1.5 mm.⁸ Using California data from 1988 to 2007, it was shown that Hispanic patients of lower SES had higher risk of thick tumors (>2 mm) than Hispanic patients of high SES, and patients with low SES had higher rates of the nodular melanoma subtype.⁹

The most common body sites for melanoma historically have included the trunk, head, and neck in men and extremities in women.¹⁰ Caini et al¹¹ found that nevus count >25 was associated with melanoma on usually nonexposed sites, such as the legs or trunk. In addition, skin and hair color correlate with body site for melanoma, which may be attributed to genetic variability.¹¹ Recent studies have found a left-sided predominance for skin cancers, including melanoma, possibly related to poor ultraviolet A–filtering side windows in automobiles.¹²

Mortality

According to data from the Connecticut Tumor Registry between 1950 and 2007, mortality rates more than tripled in men (1.6 to 4.9 per 100,000) and doubled in women (1.3 to 2.6 per 100,000).³ From 1992 to 2002 in the United States, women had

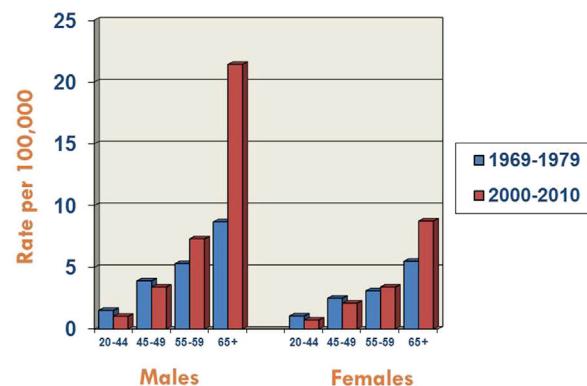


Fig 1. United States melanoma mortality among non-Hispanic whites, 1969 to 1979 and 2000 to 2010, by age and sex. (Data from the Surveillance, Epidemiology, and End Results [SEER] Program [www.seer.cancer.gov]. SEER*Stat Database: Mortality - All COD, Aggregated With State, Total U.S. [1969-2010] <Katrina/Rita Population Adjustment>, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2013. Underlying mortality data provided by NCHS [www.cdc.gov/nchs]).

reduced melanoma mortality, while men did not. In fact, between 1990 and 2006, melanoma was 1 of only 3 cancers in men where mortality rates have increased.¹³ For any given stage and across all ages, men have had poorer melanoma survival than women, with both genetic and behavioral factors proposed to explain these findings.^{14,15} More than 50% of all melanoma deaths are in white men 50 years of age and older.⁴ Lower education level and SES are also associated with decreased survival.^{16,17} Mortality rates in the United States are shown in Fig 1.

International trends

There has been a global trend of increasing melanoma incidence in people of European descent.¹⁸ Interestingly, Croatia has 1 of the highest increases in melanoma incidence—a 4-fold increase over the past 40 years—although variations in reporting may explain part of this increase.¹⁹ There were >20,000 melanoma deaths in Europe in 2008 (Fig 2), with Central and Eastern Europe having the largest share (35.5%) among the 4 geographic European regions.²⁰ Melanoma mortality remains the highest in Australia and New Zealand, where the incidence is 40 to 60 cases per 100,000 inhabitants.¹⁸

HIGH-RISK GROUPS

Key points

- **Nodular melanoma subtype tends to elude early detection because of its rapid growth and frequent amelanotic coloration**

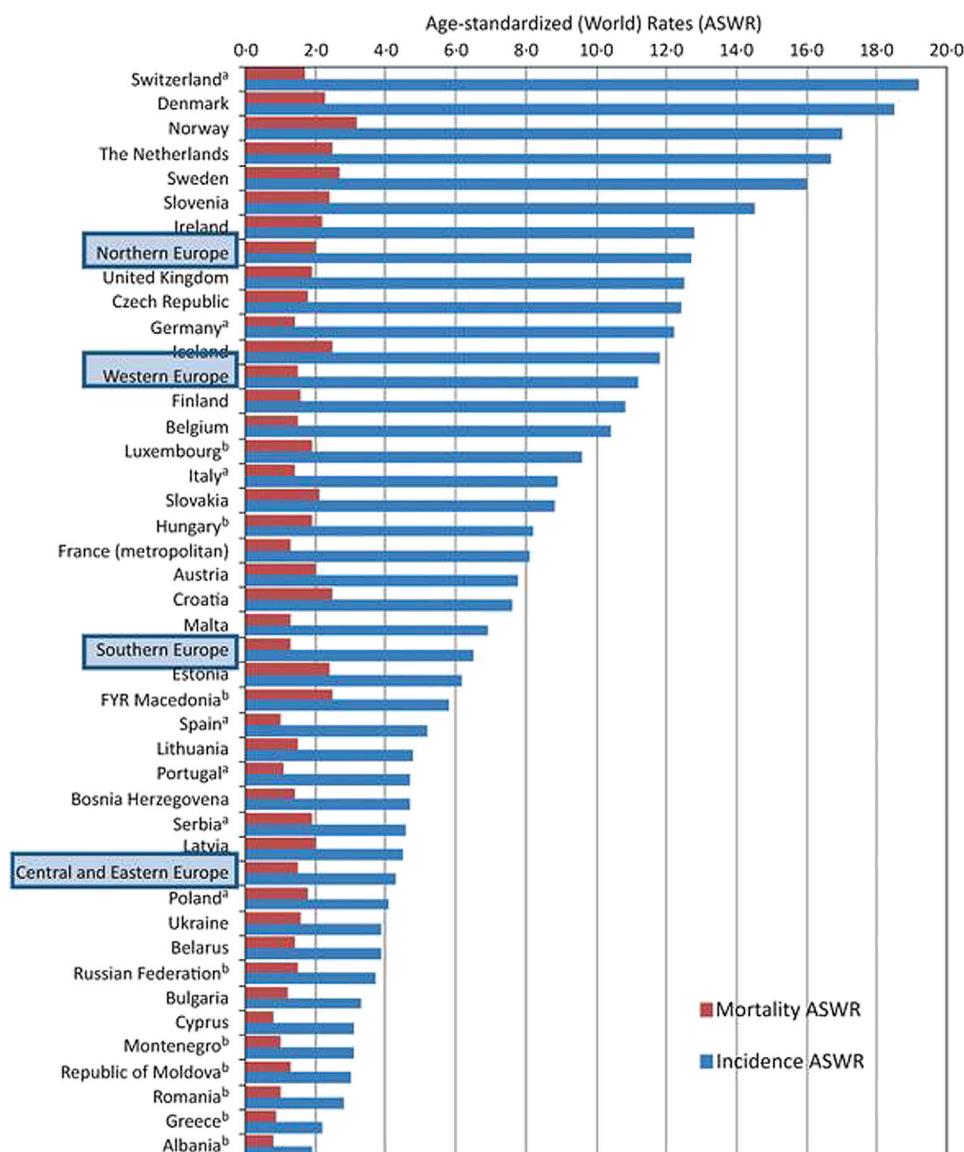


Fig 2. Estimates of incidence and mortality rates of melanoma in Europe, 2008, measured as cases per 100,000 residents. Blue columns indicate melanoma incidence age-standardized world rates (ASWRs). Red columns indicate melanoma mortality ASWRs. ^aCountries with no national cancer registries but with regional registries. ^bCountries with no national/regional registry, where estimates were made through modelling from neighboring countries. (Reprinted with permission from Forseea et al.²⁰)

- Novel risk factors for melanoma include the melanocortin-1 receptor genotype, childhood cancer history, immunosuppression, indoor tanning, and potentially Parkinson disease

Role of melanoma subtype

In terms of histologic subtypes of melanoma, the nodular subtype accounts for only 14% of all melanomas, but comprises a high percentage (37%) of fatal cases.²¹ Based on the US Surveillance Epidemiology and End Result (SEER) data from

1992 to 2004, T4 (>4 mm) melanoma increased by 3.86% annually, with individuals in the lowest SES groups and those ≥ 65 years of age having the largest percent increases in these thick tumors. However, this increase in thick tumors was not associated with a disproportionate increase in nodular melanomas, which are characterized by rapid growth that tends to preclude early detection.⁵

In comparing melanoma diagnosed in the 21st century with melanoma diagnosed between 1972 and 1982, improvements have been made in the

early detection of superficial spreading melanoma but not nodular melanoma. Superficial spreading melanoma is typically diagnosed when thinner and has lower rates of ulceration, as opposed to nodular melanoma.²² Previous data established that nodular melanoma is often detected at ≥ 2 mm, and a 2009 study of the cancer registry in Queensland, Australia further classified those at risk for thick nodular melanoma: men, older individuals, and those who had not been screened by a physician in the past 3 years.²³

Novel risk factors

Melanoma screening and educational efforts are generally targeted to individuals with established and identifiable risk factors. While the following novel risk factors are not as common, they represent a growing burden that may require innovative educational and behavioral interventions.

Melanocortin-1 receptor. The contribution of melanocortin-1 receptor (MC1R) gene variants to the development of early onset melanoma is unknown. In an Australian population-based, case-control-family study, MC1R sequencing of 565 young (18-39 years) patients with invasive cutaneous melanoma, 409 unrelated controls, and 518 sibling controls revealed that some MC1R variants were important determinants of early onset melanoma, with strong associations in men and those with none or few nevi or with high childhood sun exposure.²⁴

Childhood cancer history. A history of cancer in childhood is a risk factor for subsequent malignancy, primarily basal cell carcinoma. An analysis of childhood cancer survivors for subsequent melanoma risk revealed a standardized incidence ratio (SIR) of 2.42 (95% confidence interval [CI], 1.77-3.23).²⁵ The childhood cancer cases were generally those treated with radiation.^{25,26}

Using the Children's Oncology Group guidelines, the National Cancer Institute recommends that adult survivors of childhood cancer treated with radiation receive an annual dermatologic examination.²⁷ However, Nathan et al²⁸ found that the compliance with these recommended physician skin examination guidelines among their sample of nearly 5000 high-risk patients was only 26.6%.²⁸

Immunosuppression. Organ transplant recipients undergo long-term immunosuppression to prevent graft rejection. While transplant patients are at far greater risk of squamous cell carcinomas, they also develop more melanomas compared to the general population.²⁹ The age-adjusted incidence rate of melanoma among renal transplantation recipients was 55.9 diagnoses per 100,000 population,

representing a 3.6-fold greater risk in age-adjusted, standardized risk from the SEER population.³⁰

HIV infection has also been linked with melanoma risk. Comparing HIV infected individuals with demographically similar individuals who were not infected with HIV, Silverberg et al³¹ found elevated risks of melanoma (relative risk [RR] = 1.8 [95% CI, 1.3-2.6]).³¹

Parkinson disease. A large systematic metaanalysis reviewed the association of Parkinson disease (PD) and melanoma and found an increased RR of 1.56 (95% CI, 1.27-1.91).³² A more recent publication showed a significant relationship in cases where PD preceded melanoma, with an odds ratio (OR) of 3.61 (95% CI, 1.49-8.77). Conversely, if melanoma preceded PD, the OR was reported as 1.07 (95% CI, 0.62-1.84).³³ Interpretation of these case control studies pose limitations, and well-conducted prospective studies are needed for improved understanding of a potential biologic PD and melanoma association.

Indoor tanning/artificial sunlamps. Indoor tanning is believed to be the major contributor to the increasing incidence of cutaneous melanoma among young women. A recent metaanalysis by Wehner et al³⁴ found that the prevalence of ever exposure to indoor tanning across the United States, Europe, and Australia was 35.7% for adults, 55.0% for university students, and 19.3% for adolescents. The population proportional attributable risk was 2.6% to 9.4% for melanoma, corresponding to $>10,000$ melanoma cases each year in the aforementioned countries. An increased risk of melanoma has been associated with increasing years, hours, and sessions of tanning behavior.³⁵ A 2011 case control study in Minnesota found that ever-users of sunbeds had a 41% increased melanoma risk compared with never-users. When further subdivided, those who used sunbeds >10 times had a higher risk (OR, 2.01 [95% CI, 1.22-3.31]), as did those with earlier age of first use. Alarmingly, in a single study in Australia, 76% of melanomas in fair-skinned participants who were 18 to 29 years of age were attributed to tanning bed use at young ages.³⁶ A metaanalysis of 27 studies found an overall summary RR for melanoma of 1.20 (95% CI, 1.08-1.34) for ever use of sunbeds compared to those without this exposure. The RR for melanoma was even higher if first use of sunbeds occurred before age 35 years (RR = 1.87 [95% CI, 1.41-2.48]).³⁷

CLINICAL STRATEGIES FOR EARLIER RECOGNITION AND IDENTIFICATION

Key points

- Tools that have been used for melanoma recognition include the ABCDE clinical

warning signs, the “ugly duckling” sign, and visual aids (ie, photographs)

- **Melanoma risk assessment aids have been developed based on various risk factors to identify individuals at higher risk**
- **The use of risk assessment tools may increase the yield of targeted screening for early melanoma detection and has the potential to reduce low-yield screening by as much as 50%**

Recognition patterns

The asymmetry, border, color, and diameter (ABCD) clinical warning signs for differentiating melanoma from benign moles were developed in the 1980s. Since then, an E(evolution) and other new approaches and techniques for earlier diagnosis have been added.³⁸ The ABCDE signs of melanoma have been criticized for their inability to detect more rapidly growing melanomas, such as the nodular subtype. Because the median duration of detection of nodular melanoma is estimated to be only 5 months compared with 9 months for the superficial spreading subtype, some authors have proposed a greater focus on lesion evolution to improve early detection of the nodular subtype.²² Criticism of the D (diameter >6 mm) criterion results from data showing that almost one-third of melanomas in a dermatology practice had an initial diameter of ≤ 6 mm.³⁹ Moreover, many benign lesions, such as seborrheic keratoses and atypical nevi, exceed 6 mm in diameter, are asymmetric, or vary in color.

Similar to the emphasis on an evolving lesion, the concept of the “ugly duckling” sign focuses on identifying individual lesions that do not match a person’s typical nevus phenotype. Scope et al⁴⁰ found that the sign had a 89% sensitivity for general dermatologists, 88% for dermatology nurses, and 85% for nonclinicians. Pattern recognition may rely on clinicians’ intuition and is an important area of focus in training examiners; Wazaefi et al⁴¹ found that trained dermatologists and nonexperts alike are able to classify an individual patient’s nevi pattern into a few groups, theoretically allowing the recognition of lesions that do not fit into such a “family.” In addition, images of atypical moles and melanomas may play a role in training the public to recognize clinical warning signs of melanoma.^{42,43}

Risk-assessment aids

Self-assessment for melanoma risk factors has been shown to be inaccurate,⁴⁴ and evidence-based assessment tools are necessary to identify individuals at high risk for melanoma. Several risk assessment tools have been used, although no

available models target those at highest risk of developing lethal melanoma. Preliminary components of such a model include targeting white middle aged and older men and those without partners or significant others, who potentially play an instrumental role in early melanoma detection by assisting with skin self-inspection and prompting physician skin examinations.⁴⁵⁻⁴⁸ Unfortunately, a subset of this high-risk group may have limited access or knowledge of how to use Internet-based tools. Nevertheless, these assessment tools may also be useful to other clinicians and providers. A thorough and routine skin examination of high-risk areas, such as the back and scalp, is warranted given the disproportionate number of ultimately fatal melanomas in these locations.⁴⁹

The Melanoma Risk Assessment Tool was developed from a large case control study and is available from the National Cancer Institute (available at: <http://www.cancer.gov/melanoma/risktool/>). Calculating a person’s absolute risk of melanoma over the next 5 years up to 70 years of age, the tool incorporates inspection of the back for suspect moles and asks 2 questions about complexion and history of sun exposure.⁵⁰ A new tool developed in Australia incorporates location, common and atypical nevi, hair color, freckles, family and personal history of melanoma, and personal history of nonmelanoma skin cancer.⁵¹ The derived calculator can be accessed online (available at: <http://www.victorianmelanombservice.org/calculator/>). Another tool uses the melanoma risk score from a metaanalysis that was tested in an Italian population and externally validated in a Brazilian population. The score takes into account common nevi, skin and hair color, freckles, and sunburns.⁵²

In another model for white patients between 35 and 74 years of age, Williams et al⁵³ found that the most predictive risk factors were male sex, older age, a higher number of severe sunburns between 2 and 18 years of age, lighter natural hair color at 15 years of age, a higher density of freckles on the arms before 20 years of age, a higher number of raised moles on both arms, and previous nonmelanoma skin cancer. The validated area under the receiver operating characteristic curve of 0.70 for these variables indicates that the model predicts melanoma moderately well. Screening for melanoma in the top 15% risk category would capture a relatively high proportion of melanomas (up to 50%, if the screening examination was highly sensitive).⁵³

Finally, another recent model using mathematical e-functions was derived from an open prospective point-prevalence study of >108,000 consecutive patients presenting to dermatologists for a total

skin check. The model had 92% sensitivity for melanoma and a specificity of 67% for skin cancer in general. Although the model identified one-third of the study population as being at risk for the development of melanoma and squamous cell cancer, its use could also reduce the number needed to be screened to diagnose a single melanoma by 50%.⁵⁴

NEW TECHNOLOGIES

Key points

- Dermatoscopy increases the sensitivity of clinical evaluation for melanoma and has been shown to decrease the number of excised benign lesions
- Total body photography may supplement dermatoscopic evaluation for early detection and aid in skin self-examination
- Confocal microscopy requires specialized training and may be superior to dermatoscopy for the detection of subclinical melanoma
- While new diagnostic technologies, such as MelaFind and SIAscope, are encouraging, they substitute higher sensitivity for lower specificity
- Smartphone applications vary widely in their diagnostic accuracy and are not yet deemed reliable for early melanoma detection

Recent advances in imaging technologies could potentially lead to improved, more accurate diagnosis of melanoma. We highlight metaanalyses, randomized trials, and other comparison studies examining dermatoscopy, total body photography (TBP), confocal microscopy, and other new diagnostic aides published since the last review (Table I).¹⁷

Dermatoscopy

Dermatoscopy is now the most widely used, most studied diagnostic aid, with Kittler et al⁵⁵ and Bafounta et al⁵⁶ showing that dermatoscopy improves diagnostic accuracy, especially in the hands of dermatologists and others who frequently perform skin examinations. A metaanalysis of dermatoscopy studies performed in clinical settings found that following appropriate training, dermatoscopy increased the average sensitivity of diagnosis from 74% ("naked eye") to 90%, without a significant decrease in specificity.⁵⁷ Carli et al⁵⁸ showed that combined visual inspection and dermatoscopic examinations resulted in fewer biopsy samples being obtained. Zalaudek et al⁵⁹

found that while dermatoscopy increases the time needed for a complete skin examination by an average of 72 seconds, the total examination required <3 minutes, which the authors felt was an acceptable tradeoff for increasing pigmented lesion detection accuracy.⁵⁹ Similar findings were observed in the primary care setting: Herschorn⁶⁰ found that dermatoscopy in the hands of family practitioners increased sensitivity for melanoma without reducing specificity, and Menzies et al⁶¹ found that dermatoscopy decreased the number of benign lesions excised or referred for care by 63.5%.

With dermatoscopy in widespread use and the rise of teledermatology, many investigators are developing algorithms for analyzing digital dermatoscopy images.⁶² Bourne et al⁶³ proposed combining clinical features with dermatoscopy findings into 1 algorithm and found that this combined algorithm had a higher sensitivity than other established algorithms for melanoma, such as the 3-point checklist (previously evaluated by Gerelli et al⁶⁴) or the Menzies method, though the Menzies method was equal in diagnostic accuracy.

Total body photography (TBP)

The use of TBP is also increasing, but the clinical evidence behind this technology is still limited, and formal criteria to define suspicious lesions identified through TBP are lacking. Goodson et al⁶⁵ compared TBP to serial dermatoscopy and found that TBP was associated with lower biopsy rates than serial dermatoscopy, concluding that it was better able to detect de novo melanomas. More recently, a small, single-center study by Rademaker et al⁶⁶ found that melanomas found through TBP with sequential digital dermatoscopy were thinner than melanomas found via traditional screening methods. Salerni et al⁶⁷ studied this "2-step method" in a larger cohort of high-risk patients and found that after 10 years of regular follow-up with both dermatoscopy and photography, nearly 40% of melanomas diagnosed corresponded to lesions not under initial dermatoscopic surveillance, indicating that the combined methods increased detection. TBP remains limited by cost, insurance reimbursement policies, and access, but likely will continue to increase in accessibility and, with additional study and careful patient selection, may prove to a useful adjunct technology in monitoring high-risk patients.

Confocal microscopy

The evidence for confocal scanning laser microscopy (CSLM) in the clinical setting is still growing. CSLM uses a low power laser that reflects

Table I. Summary of new technologies for the detection of melanoma

Technology	Definition	Pros	Cons	Sensitivity	Specificity	Reference
Dermatoscopy	Examination of skin with dermatoscope	Fewer biopsy specimens and removal of benign lesions	Increases examination time and requires clinician training	90%	90%	Vestergaard et al 2008
Total body photography	Series of photographs of all skin on body	Can detect thinner tumors than the naked eye and lower biopsy rates than serial dermatoscopy	Expensive	75%	74%	Drugge et al 2009
Confocal microscopy	Low power laser that creates 3-dimensional image with resolution comparable to standard histology	Able to detect subclinical disease in an area wider than that of dermatoscopy	Limited by expense and the need for specialized training	90%	86%	Hofmann-Wellenhof 2009
MelaFind	Multispectral device that uses automated software for image analysis	High sensitivity	Expensive and low specificity	96-98%	0-10%	Monheit et al 2009
Electrical impedance spectroscopy	Device that measures changes in tissue impedance to low voltage current flow	High sensitivity	Expensive, low specificity, requires presoaking of the lesion in saline, increases examination time	98%	25-49%	Mohr et al 2013, Aberg et al 2011
Smartphone apps	Cell phone programs that analyze self-taken photographs of suspicious lesions	Widely available, and some apps send photos to Board-certified dermatologists	Experimental and highly variable quality	7-98%	30-94%	Wolf et al 2013

off structures in the epidermis and creates a 3-dimensional image, with resolution comparable to standard histology, and according to 1 review, an estimated sensitivity and specificity of 90% and 86%, respectively.⁶⁸ As with digital dermatoscopy image analysis, various algorithms have been proposed for the interpretation of these images.⁶⁹ The use of CSLM is still limited by expense and the need for specialized training, and the criterion standard for lesion diagnosis remains standard histologic examination. However, Guitera et al⁷⁰ showed its potential in the clinical setting by comparing differences in margins of lentigo malignas as identified by dermatoscopy versus confocal microscopy: CSLM was able to detect subclinical disease <5 mm beyond the dermatoscopy margin, which is beyond the standard excision margin for these lesions.⁷⁰ As the technology develops and large-scale studies are completed, CSLM may eventually reduce the number of benign biopsy specimens and provide additional information on the true margins of a particular lesion that may change management.

Novel diagnostic aids

Other diagnostic aids are still under investigation. SIAscope (Biocompatibles, Farnham, Surrey, UK), a multispectral device, provides measurements of melanin, blood, and collagen in the epidermis and papillary dermis. However, Haniffa et al⁷¹ showed that its sensitivity and specificity was similar to that of dermatoscopy by experienced dermatologists. MelaFind (MELA Sciences, Inc, Irvington, NY) is another multispectral device that uses automated software for image analysis and provides a recommendation on whether to obtain a biopsy specimen of a given lesion. Monheit et al⁷² conducted a multisite study using MelaFind to analyze 1632 lesions; the authors found MelaFind has a sensitivity of 98.4% and specificity of 9.9%, which they stated was superior to that of expert clinicians using dermatoscopic images. The low specificity and MelaFind's upfront cost and per-use fee of \$150 per image (not covered by insurance) likely will limit its use. Moreover, Wells et al⁷³ compared sensitivity and specificity of dermatologists evaluating Internet-based images and MelaFind. In that smaller study, MelaFind had a sensitivity of 96% and specificity of 8%. The authors concluded the device, similar to clinicians' examinations, trades high sensitivity for lower specificity.⁷³ Electrical impedance spectroscopy, such as the SciBase II device (SciBase AB, Stockholm, Sweden), uses tiny electrodes to measure tissue impedance to current flow. Studies have shown

high sensitivity, but specificity varies from 25% to 49%. The technology also requires presoaking the area in saline, and full lesion measurements can take several minutes.^{74,75}

Ferris et al⁷⁶ reviewed dermatoscopy, photography, and CSLM and several newer technologies, including optical coherence tomography, RNA microarray analysis of tape-stripped epidermal cells, and others. The authors noted ongoing challenges to widespread implementation of newer technologies, including the time needed to train users, efficiency of use, and significant cost barriers, including the lack of insurance coverage.⁷⁶

Finally, smartphone applications—a widely available imaging modality—are of interest in pigmented lesion analysis. However, these remain experimental: Wolf et al⁷⁷ recently evaluated 4 applications and found that sensitivity ranged from 6.8% to 98.1% and specificity from 30.4% to 93.7%. An app designed to send images to a Board-certified dermatologist had the highest sensitivity. The authors concluded that the performance of such applications is highly variable and unreliable.⁷⁷

In conclusion, the rising incidence and unremittingly high melanoma mortality rates make melanoma a central concern for developed countries. In addition to identifying new high-risk groups, new risk assessment aids and diagnostic technologies have been created that have potential to increase early detection while reducing the burden of unnecessary procedures. While these advances highlight areas of opportunity for earlier detection of melanoma, they are best viewed as adjunct tools to a complete skin examination by a trained clinician, which remains the criterion standard for detection.

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Answers to CME examination

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Screening, early detection, education, and trends for melanoma: Current status (2007-2013) and future directions

Part II. Screening, education, and future directions

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After completing this learning activity, participants should be able to describe the benefits of physician screening and counseling for melanoma and

describe the evidence for skin self-examinations based on the latest literature available.

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New evidence has accumulated over the past several years that supports improved melanoma outcomes associated with both clinician and patient screening. Population-based and workplace studies conducted in Australia and the United States, respectively, have shown decreases in the incidence of thick melanoma and overall melanoma mortality, and a year-long statewide screening program in Germany has shown a nearly 50% reduction in mortality 5 years after the screening ended. Current melanoma screening guidelines in the United States are inconsistent among various organizations, and therefore rates of both physician and patient skin examinations are low. As policymaking organizations update national screening recommendations in the United States, the latest research reviewed in part II of this continuing medical education article should be considered to establish the most effective recommendations. Patient and provider education will be necessary to ensure that appropriate patients receive recommended screening. (J Am Acad Dermatol 2014;71:611.e1-10.)

Since the most recent review of screening studies (2007)¹ and the recommendations of the US Preventive Services Task Force (2009),² there have been notable advances in the effectiveness of screening in reducing melanoma mortality and tumor thickness, the penetration of screening efforts led by dermatologists worldwide, and the development of new interventions to improve both physician and self-screening. After discussing current screening guidelines and rates of screening, we explore several interventional and observational studies that appear to support screening, many of which have led to decreased mortality and thinner melanomas (Table I).

SCREENING GUIDELINES

Key points

- The current guidelines provide inconsistent messages regarding the pros and cons of screening for melanoma
- A growing pool of evidence points to the potential for screening to improve melanoma outcomes
- Recommendations from the US Preventive Services Task Force and other organizations are crucial to ensure that appropriate patients receive regular screening and education

Screening guidelines for skin cancer are contradictory and confusing for the general public and practitioners alike. The American Cancer Society recommends that primary care physicians (PCPs) check for skin cancer “on the occasion of a periodic health examination” for men and women ≥ 20 years of age.³ On the other hand, the American Academy

Abbreviations used:

INFORMED:	Internet-based Program for Melanoma Early Detection
NHIS:	National Health Interview Survey
PCP:	primary care physician
PSE:	physician skin examination
RR:	relative risk
SCREEN:	Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany
SEER:	Surveillance Epidemiology and End Results
SSE:	skin self-examination
USPSTF:	United States Preventive Services Task Force

of Dermatology recommends that patients perform skin self-examinations (SSEs) but, in regard to physician skin examinations (PSEs), does not specify who should get screened or how often.⁴

The most recent skin cancer screening guidelines from the US Preventative Services Task Force (USPSTF) in 2009 recommend that clinicians “remain alert” for potentially malignant skin lesions during a physical examination for other reasons.² While numerous worldwide studies have shown that physician detection of melanoma is associated with thinner tumors at the time of diagnosis,⁵ no randomized trials have established the efficacy of clinician screening for melanoma on mortality reduction. As such, the 2009 statement from the USPSTF found insufficient evidence to recommend either for or against routine skin cancer screening of the general population by PCPs or SSEs.² However, there is mounting evidence for improved melanoma outcomes with clinician skin

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Table I. Key studies and major findings

Authors (y)	No. of subjects	Time period	Premise	Major finding(s)	Screener (dermatologist or PCP)
Schneider et al ¹⁸ (2008)	Thousands	1984-1996	Employee screening program at the Lawrence Livermore National Laboratory in Northern California	69% reduction in thick melanoma (>0.75 mm); no melanoma mortality in the study workforce compared with 3.39 expected deaths (based on California mortality data; $P = .034$)	Dermatologist
Aitken et al ²¹ (2010)	7586	2000-2003	Population-based, case control study of Queensland, Australia residents (20-75 years of age) with histologically confirmed first primary invasive melanoma	14% lower risk of thick (>0.75 mm) melanoma diagnosis after a PSE within the previous 3 years (OR, 0.86 [95% CI, 0.75-0.98]); 26% fewer melanoma deaths in screened cases vs unscreened cases within 5 years	Both
Swetter et al ²⁴ (2012)	566	May 2006-March 2009	Multi-institutional study of adults with invasive melanoma assessed the role of PSE in the year prior to diagnosis	Patients who had a full-body PSE (dermatologist or PCP) in the year before diagnosis >2 times as likely to have a thinner melanoma (OR, 2.51 [95% CI, 1.62-3.87]); men >60 years of age who had PSE 4 times as likely to have thinner melanoma (OR, 4.09 [95% CI, 1.88-8.89])	Both
Katalinic et al ¹⁵ (2012)	360,288	July 2003-June 2004	All citizens in Schleswig-Holstein, Germany, ≥ 20 years of age with statutory health insurance were eligible for a standardized PSE	47% and 49% decline in mortality for men and women, respectively; mortality decline in Schleswig-Holstein significantly different from mortality rates in 4 unscreened adjacent regions and rest of Germany, where mortality rates were stable	Both

CI, Confidence interval; OR, odds ratio; PCP, primary care physician; PSE, physician skin examination.

screening that may prompt a reanalysis of the worldwide data by the USPSTF. A USPSTF recommendation for skin screening could have a large impact on clinical practice in the United States, because language in the Affordable Care Act mandates that all USPSTF recommendations of grade B and above must be adopted within 12 months of the new ruling.

RATES OF PHYSICIAN SCREENING

Key points

- Rates of annual clinician skin examinations range from 8% to 21%
- A metaanalysis of 9 US studies found that the proportion of primary care physicians who perform such examinations decreased between 1987 and 2004

Based on patient surveys, the documented prevalence of annual clinician skin examinations ranges from 8% to 21%.⁶⁻⁸ Data from the National Ambulatory Medical Care Survey showed that patients had a higher chance of receiving a skin examination (and also most general medical screening) if they saw a physician assistant or nurse practitioner than if they saw a physician, which was attributed to physicians more often being tasked with addressing acute complaints and chronic illness visits rather than routine screening visits.⁹ In a random sample of 10,486 people (aged ≥ 50 years) from the 2005 National Health Interview Survey (NHIS), 16% of men and 13% of women reported having a PSE in the previous year. Using multivariate techniques, the lowest skin examination rates were associated with

younger age (50-64 years), lower education level, lack of previous skin cancer, and lack of other screening (eg, colorectal).¹⁰ Data extrapolated from the 2010 NHIS indicate that about 105 million (51%) US adults are at high risk for developing melanoma (based on the USPSTF criteria,² including age, race, sunburns, and family history), of which 24% had at least 1 total body PSE.¹¹ In a survey of 1600 physicians, time constraints, competing comorbidities, and patient embarrassment were reported as the top 3 barriers to performing full skin examinations. Factors that facilitated skin screening among all physicians included having patients at high risk for skin cancer, patient demand for complete examination/mole check, and the influence of medical training.¹² A metaanalysis that included 9 studies from the United States found that the proportion of PCPs who perform full body skin examinations for screening decreased over time between 1987 and 2004¹³; definitions of screening may have changed during that time, which could have influenced the results.

SCREENING AND EARLY DETECTION

Key points

- The implementation of a year-long statewide screening program in Schleswig-Holstein, Germany was associated with a nearly 50% reduction in mortality
- An employee screening program at the Lawrence Livermore National Laboratory in California found a reduction in thick melanoma and melanoma mortality
- A population-based, case control study in Queensland, Australia revealed a reduction in the incidence of thick melanoma and estimated melanoma mortality
- Physician- or other health practitioner-detected melanoma results in thinner melanomas than does family- or self-detection
- A multi-institutional study of adults in the United States with invasive melanoma found that full-body physician skin examination was associated with thinner melanomas, especially in men >60 years of age

Population-based screening programs

A landmark study was conducted between July 2003 and June 2004 (first reported in 2009) in Schleswig-Holstein, Germany (ie, the Skin Cancer Research to Provide Evidence for Effectiveness of Screening in Northern Germany [SCREEN] project. Of 1.88 million eligible citizens, 360,288 participated in SCREEN (a participation rate of 19%). All citizens ≥ 20 years of age with statutory health insurance were eligible for a standardized whole-body

examination during the 12-month study period. After receiving a mandatory 8-hour training program, physicians were eligible to receive upward of €30 for each screening examination performed. Seventy-seven percent of patients chose to be first screened by a general practitioner trained in skin examination; the rest chose to be screened directly by a dermatologist. Forty-nine percent of participants were ≥ 50 years of age. Twenty-six percent had either a suspicion of skin cancer or were considered at increased risk for skin cancer, and 9% of participants had a personal or family (first-degree) history of melanoma. A total of 3103 malignant skin tumors were found. Between 2000 and 2009, melanoma mortality declined by 47% from 1.9 to 1.0 per 100,000 men, and by 49% from 1.4 to 0.7 per 100,000 women. The decline in mortality in Schleswig-Holstein was significantly different from the mortality rates in the 4 unscreened adjacent regions and the rest of Germany, where mortality rates were stable during the same time period (Fig 1).^{14,15}

Although the study did not provide definitive proof, it offers perhaps the strongest available evidence to date that a population-based skin cancer screening program involving both PCPs and dermatologists can lead to reduced melanoma mortality. Potential confounders, such as coding practices, primary prevention programs, therapy differences, age, and sex did not appear to be noticeably different in Schleswig-Holstein compared with other parts of Germany.¹⁵ Promising findings from the SCREEN project led to Germany-wide expansion in 2008 aimed at individuals ≥ 35 years of age.¹⁶ In 2012, 45 million Germans were eligible to be screened for skin cancer once every 2 years, and 30 million screenings have been performed to date. Researchers will be able to compare the 2008 to 2013 mortality data and beyond with contemporaneous data from Germany's 9 border countries where organized screening did not take place.

So far, response from various physician groups has been reported. The average dermatologist performed >1300 screenings annually, with a mean remuneration of about €22 per screen. Nearly two-thirds of the dermatologists were rather or very satisfied with routine PSE, and a rising number of dermatologists (83%) perceived a better quality of health care for skin cancer since the expansion in 2008.¹⁷

Workplace screening and education

An employee screening program at the Lawrence Livermore National Laboratory conducted between 1984 and 1996 revealed that increased melanoma education, self-examination, and opportunity for

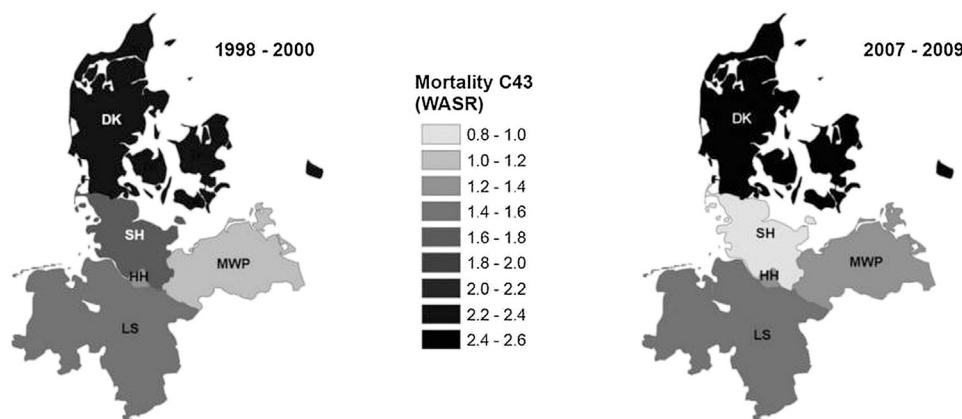


Fig 1. Observed melanoma mortality is shown in the screening area (Schleswig-Holstein [SH]) and in the 4 adjoining regions (Denmark [DK], Mecklenburg-Vorpommern [MWP], Hamburg [HH], and Lower Saxony [LS]) as the age standardized rate (World Population [WASR]) per 100,000 people. C43 indicates code C43 from the *International Classification of Diseases, 10th edition*. (Figure reprinted with permission from Katalinic et al.¹⁵)

physician skin screening resulted in a reduction in crude incidence of thicker melanomas (>0.75 mm) during 3 phases of increasing melanoma surveillance: preawareness (1969-1975), early awareness of increased melanoma risk (1976-1984), and the active screening program (1984-1996). A 69% reduction in thick melanoma diagnosis was reported in the screening program period compared to the early awareness period, with a reduction in mortality in the study workforce during this timeframe compared with California mortality data (no workplace deaths compared with expected number of 3.39 deaths [$P = .034$] based on observed mortality in 5 San Francisco/Oakland Bay area counties as reported to the SEER program between 1984-1996).¹⁸

Physician skin examinations

Because most Americans will not see a dermatologist during their lifetime, educating PCPs in at least the basic skin cancer triage has been proposed. Integration of the skin examination into a routine physical assessment by PCPs with referral to dermatologists may be a practical strategy for reducing skin cancer mortality. The patients most at risk for lethal melanoma—white males ≥ 50 years of age—are more likely to present to a PCP than to a dermatologist.

Recent data suggest that melanomas detected by clinicians through directed skin examinations or during the course of routine physical examinations (eg, “opportunistic screening”) are thinner than those found by patients or their significant others.¹⁹⁻²³ In an analysis of 9 worldwide studies of >7500 patients, melanomas detected by physicians were 0.55 mm thinner than those detected by patients or significant others.⁵

Since the 2009 USPSTF recommendations, strong evidence for improved melanoma outcomes with physician skin screening was reported in a population-based, case control study by Aitken et al²¹ of Queensland residents (20-75 years of age) with histologically confirmed first primary invasive melanoma diagnosed between January 2000 and December 2003. This study noted a 14% lower risk of thick (>0.75 mm) melanoma diagnosis for those reporting a clinician skin examination within the previous 3 years compared to those without such an examination (odds ratio [OR], 0.86 [95% confidence interval {CI}, 0.75-0.98]). The decrease in risk was greatest for the thickest melanomas (risk reduction 40% for lesions ≥ 3 mm), resulting in a projected 26% decrease in melanoma deaths in screened compared to unscreened cases within 5 years.²¹

A subsequent multi-institutional study of 566 adults with invasive melanoma (interviewed in clinic within 3 months of diagnosis) assessed the role of PSEs in the year before diagnosis and found that men >60 years of age appeared to benefit the most from this practice. Thinner tumors (≤ 1 mm) were significantly associated with physician discovery ($P \leq .0001$), although this was reported by only 19% of patients. However, patients who had a full-body skin examination by a physician (dermatologist or PCP) in the year before diagnosis were more than twice as likely as patients without such an examination to have a thinner melanoma (OR, 2.51 [95% CI, 1.62-3.87]), largely because of the effect of PSEs in men >60 years of age, who had 4 times the odds of a thinner melanoma (OR, 4.09 [95% CI, 1.88-8.89]). Thinner tumors were also associated with age ≤ 60 years, female sex, and higher education level.²⁴ Looking only at men ≥ 40 years of age, thinner

tumors were associated with the presence of atypical nevi, higher education (high school and above), and physician discovery. Increased melanoma knowledge, interest in health topics, and knowledge of the importance of PSE were also associated with thinner tumors.²⁰

Pollitt et al²⁵ analyzed enrollment in the California Medicaid program and correlations with melanoma tumor thickness. They found that men and women who were intermittently enrolled in Medicaid or not enrolled until the month of diagnosis had a greater chance of late stage melanoma compared with other patients. Patients continuously enrolled in Medicaid during the previous year did not have higher rates of late stage melanoma, suggesting greater access to screening services in this subset. In a study using data from the National Cancer Database, patients only covered by Medicare were shown to have a lower risk of stage III and IV melanoma than uninsured patients.²⁶

Sex-specific patterns may influence decision-making in the care seeking process for suspect lesions.²⁷ Andruson et al²⁸ sought to understand how age and sex influence screening behavior by surveying 487 patients (59.2% were female; 54.0% were ≥ 50 years of age) attending skin cancer screening. Compared with men, women were more likely to seek screening because of a concerning lesion (24.6% vs. 11.9%) and because of concern over previous sun exposure (34.3% vs. 23.8%).²⁸

Dermatologist-led mass screening programs

Euromelanoma is a dermatologist-led skin cancer prevention program that involves annual screening and public education campaigns in more than 20 European countries. In its first 10 years, Euromelanoma screened >260,000 individuals and promoted awareness of melanoma and its risk factors. Of the nearly 60,000 individuals screened in 2009 and 2010, most were female (64%), the median ages were 43 years (for women) and 46 years (for men), and 33% had Fitzpatrick skin phototypes I or II. Dermatoscopy was used in 78% of examinations with clinically suspected melanoma; full-body PSEs were performed in 72% of patients. The suspicion rate for melanoma ranged from 1.1% to 19.4% (average, 2.8%), and the overall positive predictive value was 13%. Melanoma detection rates varied from 0.1% to 1.9%.²⁹

Dermatologist office-based screening

Durbec et al³⁰ retrospectively studied 650 patients in France who were seen by a dermatologist for melanoma. The thinnest tumors were seen in patients seeing a dermatologist for prospective follow-up of nevi and in patients consulting a

dermatologist for another disease. Patients who first saw a general practitioner tended to be older and had the highest frequency of thick (>3 mm), nodular, and/or ulcerated melanoma, which could be interpreted as a need to promote the PCP role in melanoma screening and triage, because more "advanced" cases present to the generalist over the specialist.³⁰

In a multicenter study of 14,381 consecutive patients, Argenziano et al³¹ found that PSEs for patients presenting with localized dermatologic problems allowed for the detection of melanomas that would otherwise be missed at a rate of 1 melanoma per 400 patients.³¹ Additional evidence for the importance of opportunistic, whole-body screening during routine physical examination was shown in a case series of melanoma patients from a dermatology practice in Florida,²² in which increased detection of thinner melanomas and melanoma *in situ* were noted through full-body skin examination rather than patient complaint of a suspicious skin lesion.

Goodson et al³² studied 572 melanoma cases over a 10-year period to determine which factors were associated with delayed detection. In established patients, melanomas were detected at twice the rate and at an earlier stage compared with those in new patients, which may be attributed to those with a history of melanoma being at higher risk for a second primary melanoma and undergoing increased surveillance.³²

Investigating the effectiveness of screening patients at increased risk for melanoma, Shore et al³³ conducted a retrospective study of about 18,000 patients screened over a 17-year period at a private dermatology practice. They found that all melanomas were diagnosed at ≤ 0.15 mm, and there were no deaths, metastases, recurrences, or need to obtain sentinel node biopsy specimens. In addition to performing thorough skin examinations and obtaining biopsy specimens of suspicious lesions, the authors attributed their success to recalling patients every 6 months and educating them on the importance of returning for future examinations.³³

Specialized pigmented lesion clinics

Established pigmented lesion clinic patients (defined as receiving care at the clinic for ≥ 3 months) had more *in situ* disease (70% vs. 57%; $P < .001$), thinner invasive melanomas (0.45 mm vs. 0.82 mm; $P = .002$), and a lower incidence of ulceration than new patients.²³ Lipworth et al³⁴ studied the addition of an urgent access track within a pigmented lesion clinic. Urgent access track patients ($n = 316$) were 4 times more

likely to be diagnosed with melanoma than regular patients ($n = 4495$; OR, 4.24 [95% CI, 2.28-7.88]).³⁴

Skin self-examinations

Effective self-identification of melanoma is dependent on several factors, including increased public and health professional awareness and knowledge of the SSE practices, the health provider teaching of the SSE to patients, and consistent performance of SSE by patients. The American Cancer Society recommends thorough SSEs of all body areas, including the back, back of the legs, and scalp—areas that are typically difficult to self-inspect.³ While the USPSTF described insufficient evidence to recommend SSEs or PSEs for the general population in its 2009 report, the potential benefit in high-risk groups such as older men was noted.²

In a study of 321 melanoma patients, Pollitt et al³⁵ showed that the thoroughness of SSE, as measured by the number of body sites examined and use of a picture aid illustrating a melanoma, was the best predictor of reduced melanoma thickness. Thinner tumors were observed in patients who frequently examined at least some of their skin in the year before melanoma diagnosis (OR, 2.66 [95% CI, 1.48-4.80]), and the effect of SSE was even greater in men and in older patients (>60 years of age).³⁵

Despite the potential benefit of SSE for early melanoma detection, the prevalence of SSE in the general population is low. It is estimated that only 10% to 25% of individuals in the United States practice regular thorough SSEs.³⁶ For higher risk populations, various educational programs have successfully increased SSE performance.^{37,38} Other studies have noted that patient and partner intervention with tailored information, using computer or video training along with telephone reminders, may increase the prevalence of SSE.^{39,40} Although concerns might exist over an individual's ability to detect atypical moles on his or her skin, a study using a crowdsourcing approach in 500 adults recruited from a shopping mall who were given an educational pamphlet led to a sensitivity and specificity of 90% and 72%, respectively.⁴¹

Populations at high risk

Several studies have sought to determine the effectiveness of screening certain high-risk populations. Comparing the ratio of the prevalence of melanoma in a selected high-risk population to the prevalence in the general population, researchers in France found that screening only the high-risk patients was 11 times more efficient,

resulting in 11 times fewer patients screened to detect the same number of melanomas.⁴²

Family members of melanoma patients. The results of the Swedish Melanoma Study Group, which assessed family members of patients with melanoma, found that familial-targeted surveillance led to the detection of tumors with more favorable prognostic characteristics, such as decreased thickness, in comparison with melanomas in the general Swedish population.⁴³ However, Oliveria et al⁴⁴ surveyed 406 US dermatologists and found that <50% routinely offered to screen nearby first-degree relatives of their melanoma patients. Multiple studies have shown that physician recommendation is positively correlated with family members receiving a PSE.^{45,46}

Many moles/atypical moles. A metaanalysis examining the population attributable fraction for melanocytic nevi determined that 42% of melanomas were attributable to having ≥ 25 nevi and led to recommending this high-risk group for special screening and education.⁴⁷ In a study of >1000 patients with previous melanoma, multivariate analyses revealed that second primary melanoma was associated with high nevus count (hazard ratio, 2.91 [95% CI, 1.94-4.35]).⁴⁸ People with atypical nevi have also been recommended for screening and education, because the presence of atypical nevi gives a 2- to 15-fold increased risk of melanoma.⁴⁹

PROFESSIONAL AND PUBLIC EDUCATION

Key points

- Educational programs to train primary care physicians regarding melanoma detection have been shown to increase appropriate diagnosis and management
- Educational videos and simulation experiences have successfully been used in training medical and nursing students in melanoma detection

Physician interventions

Because of limited dermatology resources, it is important to provide training in basic skin cancer examinations to PCPs. To this end, a recent study of general practitioners in France noted a significant benefit from training general practitioners about melanoma. Trained general practitioners were more than twice as likely as those without training to detect a patient's melanoma.⁵⁰

A number of web-based educational programs have been designed for providers, including a 1.5-hour interactive training program called the Internet-based program for Melanoma Early

Detection (INFORMED⁵¹; available at: www.skinsight.com/info/for_professionals/skin-cancer-detection-informed/skin-cancer-education). A recent US study evaluated the effect of INFORMED on 54 PCPs at 2 integrated health care delivery systems on practice patterns, including referral or visits to dermatology and skin biopsy specimens obtained during the 6 months after training. Scores for appropriate diagnosis and management increased from 36% pretraining to 47% posttraining (OR, 1.6 [95% CI, 1.4-1.9]), with the greatest improvement observed for benign skin lesions. Rates of dermatology use decreased without any change in biopsy specimens obtained or skin cancers diagnosed.⁵¹

Medical school training

Surveys show that the majority of medical students feel that their training in the skin cancer examination is limited. In 1 small study, only 22.6% of fourth-year medical students noticed a melanoma moulage on the finger of a standardized patient.⁵² Garg et al⁵³ assessed the effectiveness of an educational program directed toward melanoma detection and found that after viewing an educational film, students demonstrated an improvement in melanoma knowledge, including the ability to identify high-risk populations and sex-specific anatomic areas of increased risk. Moreover, students expressed more confidence in skin cancer examinations and their ability to integrate them into regular patient encounters.⁵³ Similarly, among a sample of 74 third-year medical students, a 1-hour melanoma simulation and skills training experience improved the students' confidence in melanoma surveillance and counseling, in addition to their management decisions regarding the observation of suspicious lesions and when to obtain biopsy specimens from those lesions.⁵⁴

Nurses

Given their close patient contact, nurses can play an important role in melanoma prevention. A review of skin cancer screening among advanced practice nurses concluded that in addition to the biggest barrier of limited time, screening is limited by their ability to differentiate suspicious and benign lesions. However, this skill improved among the nurses after training.⁵⁵ To this end, a study involving 104 nursing students used simulated lesions on standardized patients to practice evaluating and teaching early detection principles. At the end of the simulation, students' average responses to an evaluation based on program goals were positive.⁵⁶ Even for experienced nurse practitioners, a small pilot study found that an educational presentation led to increased knowledge for identifying at-risk individuals.⁵⁷

Nonclinicians

Hair professionals represent a potential "untapped resource" for the early detection of melanoma on the scalp and neck.⁵⁸ A survey of workers in 17 Texas hair salons found that 37% of respondents looked at >50% of their customers' scalps, and 29% looked at >50% of their customers' necks. Forty-nine percent of the hair professionals were "very" or "extremely" interested in participating in a skin cancer education program.⁵⁹ Chiropractors may be another resource for the detection of melanoma, especially on the neck and back. A study of 217 chiropractic students found that 86% felt it was "important" or "very important" to recognize skin cancer signs among their patients, and 66% "frequently" or "always" scan the neck or back of a patient for skin lesions on an initial examination.⁶⁰

FUTURE DIRECTIONS

Studies have shown that dermatologists are significantly better than nondermatologist physicians at diagnosing melanoma, although most suggest that tumor thickness does not appear to substantially differ by provider type. Because Americans ≥ 45 years of age make an average of 2.1 visits to PCPs each year,⁶¹ PCPs can serve as an important source of skin cancer observation, basic examination, and triage. Increasing patient demand for skin examinations—coupled with a lack of dermatologists in certain areas—means that most physician-detected melanoma is detected by PCPs compared to dermatologists, and PCPs obtain the initial biopsy specimen in 1.4% to 13% of all melanomas.⁶² Primary care providers should therefore play a key role in any comprehensive future screening program in the United States.

However, PCPs in the United States may not be adequately trained to identify early skin cancer.⁶³ Many physicians have minimal exposure to teaching of the skin cancer examination during medical school and residency. Educational initiatives for PCPs, such as the aforementioned INFORMED training program, should therefore be complementary to expansion in screening.

The previously discussed studies—such as those by Aitken et al,²¹ Schneider et al,¹⁸ and Swetter et al,²⁴ along with the German SCREEN population-based time series and the ongoing nationwide skin screening program in Germany—suggest that integration of the skin examination into a routine physical assessment by PCPs (followed by expert dermatology follow-up) may be a practical strategy for reducing skin cancer mortality. PSEs should be synergistic with SSEs for early melanoma detection.

In the SCREEN project, 45% of men and 51% of women who were screened had at least 1 defined

risk factor for melanoma.¹⁵ With a shortage of both PCPs and dermatologists in the United States, it may be most practical to prioritize screening patients who are at the highest risk of death from melanoma (ie, white patients ≥ 50 years of age).

In conclusion, whether screening is offered to all adults or limited to those with melanoma risk factors, evidence from the most recent published data will guide national recommendations that will likely change current practice. Amidst the present atmosphere of health care cost-cutting and payment reform, recommendations from the USPSTF and other organizations, such as the American Academy of Dermatology, are crucial to ensure that appropriate patients receive regular screening and education regarding melanoma. In the interim, dermatologists should continue to offer and perform PSEs in the context of routine patient visits and train PCPs in the basic skin cancer examination. A growing body of evidence now appears to tip the scales in favor of PSEs for melanoma.

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Polycystic ovary syndrome: A review for dermatologists

Part I. Diagnosis and manifestations

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After completing this learning activity, participants should be able to describe the diagnostic criteria and appropriate laboratory work-up required to make the diagnosis of polycystic ovary syndrome (PCOS); identify women who are at risk for PCOS among their patients who present with acne, hirsutism, acanthosis nigricans, and/or androgenetic alopecia; have an understanding of the pathophysiology of

PCOS; and describe the dermatologic, gynecologic, metabolic, and psychological manifestations of PCOS.

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Polycystic ovary syndrome (PCOS) is a common endocrine disorder among women who are of reproductive age. The pathogenesis involves several associated hormonal pathways that culminate in metabolic, reproductive, and cardiovascular effects. The hallmark features of hyperandrogenism and hyperinsulinemia have systemic long-term implications. Dermatologists frequently evaluate and manage the cutaneous manifestations of PCOS (ie, acanthosis nigricans, hirsutism, acne, and alopecia), and therefore play a key role in its diagnosis and management. In part I of this continuing medical education article, we review the definition, etiology, pathogenesis, and clinical features of PCOS. (J Am Acad Dermatol 2014;71:847.e1-10.)

Key words: acanthosis nigricans; acne; anovulation; hirsutism; hyperandrogenism; insulin resistance; polycystic ovary syndrome.

Polycystic ovary syndrome (PCOS) is one of the most common endocrine disorders affecting women of reproductive age. This pervasive disorder of unknown etiology is characterized by 3 fundamental features: hyperandrogenism, chronic anovulation, and ultrasonographic evidence of polycystic ovaries. Women with PCOS are at risk for multisystemic consequences, including type 2 diabetes mellitus, cardiovascular disease, endometrial cancer, obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric disorders. Clinicians involved in the care of women with PCOS should understand the potential health risks for these patients. Dermatologists are in a unique position to recognize the clinical manifestations of hyperandrogenism and insulin resistance and play an important role in the diagnosis and management of women with PCOS.

DEFINITION

Key points

- **Polycystic ovary syndrome is a common endocrine disorder that affects up to 8% of women who are of reproductive age**
- **The 2003 Rotterdam criteria requires 2 out of 3 clinical indications to make the diagnosis of polycystic ovary syndrome, including oligo- or anovulation, clinical and/or biochemical signs of hyperandrogenism, and echographic polycystic ovaries**
- **Polycystic ovary syndrome is a diagnosis of exclusion; other etiologies of hyperandrogenism and anovulation must be ruled out**
- **The etiology remains unknown, but genetics along with early androgen exposure likely play a role**

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Abbreviations used:

BMI:	body mass index
DHEA:	dehydroepiandrosterone
DHEAS:	dehydroepiandrosterone sulfate
FSH:	follicle-stimulating hormone
GnRH:	gonadotropin-releasing hormone
IGF-1:	insulin-like growth factor 1
LH:	luteinizing hormone
OSA:	obstructive sleep apnea
PCOS:	polycystic ovary syndrome
SHBG:	sex-hormone binding globulin

In 1935, Drs Irving Stein and Michael Leventhal described a phenomenon in which 7 women had anovulation and polycystic ovaries discovered during surgery.¹ The condition was called Stein-Leventhal syndrome and was later renamed polycystic ovary syndrome (PCOS) to represent the unique morphology of the ovaries. Since its initial description, 2 main definitions of PCOS have emerged. The 1990 National Institutes of Health (NIH) definition requires the presence of oligo- or anovulation and biochemical or clinical signs of hyperandrogenism. Alternatively, the 2003 Rotterdam criteria broadens this definition and requires the presence of 2 out of 3 of the following clinical indications: oligo- or anovulation, biochemical or clinical signs of hyperandrogenism, and echographic polycystic ovaries (Table I).² Importantly, both definitions require the exclusion of other conditions that result in anovulation and hyperandrogenism, such as congenital adrenal hyperplasia, Cushing syndrome, and androgen-secreting tumors. These conditions can be excluded upon the evaluation of symptoms and relevant laboratory studies (Table II). The Rotterdam criteria

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Table I. 1990 National Institutes of Health criteria and 2003 Rotterdam criteria for the diagnosis of polycystic ovary syndrome

National Institutes of Health criteria (requires all 3)
1. Chronic anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Exclusion of other causes of hyperandrogenism and anovulation, such as Cushing syndrome, congenital adrenal hyperplasia, and androgen-secreting tumors
Rotterdam criteria (requires 2 out of 3)
1. Oligo- or anovulation
2. Clinical and/or biochemical signs of hyperandrogenism
3. Echogenic evidence of polycystic ovaries and exclusion of other causes of hyperandrogenism and anovulation, such as Cushing syndrome, congenital adrenal hyperplasia, and androgen-secreting tumors

identify 4 phenotypes of PCOS, which illustrates the variable clinical features of irregular menses, hyperandrogenism, polycystic ovaries, and insulin resistance (Table III). The prevalence of PCOS among women who are of reproductive age has been estimated to be 6.5% to 8%.³ However, the prevalence varies depending on the diagnostic criteria used. Given the broader definition described in the Rotterdam criteria, the prevalence of PCOS has subsequently been noted to range from 15% to 18%.⁴⁻⁶

While the etiology of PCOS is unknown, it is theorized that gestational environment and steroid exposure likely play a role. Early exposure to androgen excess in utero or during the neonatal period is associated with the development of the PCOS phenotype later in life^{7,8}; this was shown in several primate and nonprimate animal studies.⁷⁻⁹ Rhesus monkeys that were exposed to prenatal testosterone later developed higher basal androgen levels and an exaggerated androgen response when stimulated.⁸ This was further supported by another study on female lambs that were exposed to intrauterine testosterone.⁹ Those lambs subsequently developed the PCOS phenotype during adolescence and had enlarged ovaries, irregular menstrual cycles, and hyperandrogenism. Studies on humans with congenital virilizing tumors have shown continued metabolic and reproductive abnormalities similar to the PCOS phenotype, even after treatment.⁷ These findings suggest that the hypothalamic-pituitary-gonadal axis is programmed by early androgen exposure. In addition to environmental factors, PCOS also has a genetic basis and is associated with several candidate genes for insulin resistance

and androgen production (eg, cytochrome P450c17, cytochrome P450c11a, and insulin receptor substrate 1), supporting the evidence of strong heritability of PCOS in families.¹⁰⁻¹²

PATHOGENESIS

Key points

- Patients with polycystic ovary syndrome have an increased pulsatility of gonadotropin-releasing hormone, which results in a preferential secretion of luteinizing hormone
- The hormonal pathways of polycystic ovary syndrome involve the interplay among androgens, insulin, luteinizing hormone, and estrogen, leading to broad metabolic and reproductive sequelae

PCOS is a complex disorder with several aberrant hormonal pathways resulting in reproductive and metabolic abnormalities. While the pathogenesis is not completely understood, several key hormonal pathways likely contribute. In PCOS, the hypothalamus secretes gonadotropin-releasing hormone (GnRH) at an increased pulse frequency.¹³ This increased GnRH frequency is either caused by an inherent defect in the GnRH pulse generator or to lower progesterone levels among women with PCOS. Progesterone slows the GnRH pulse generator, which explains why low levels of progesterone could increase GnRH pulsatility.¹⁴ The net increased frequency of GnRH pulsation stimulates the anterior pituitary gland to preferentially secrete luteinizing hormone (LH) over follicle-stimulating hormone (FSH).¹⁵ LH stimulates the ovarian theca cells to synthesize androstenedione. Androstenedione can either be converted to testosterone or it can be aromatized in the nearby ovarian granulosa cell and converted into estrogen via aromatase. While the theca cell is stimulated by LH, the granulosa cell is stimulated by FSH. In this setting of preferential LH secretion, the net ovarian hormonal production is an increased amount of androgen. Androgens have numerous local and systemic effects. They act locally to arrest ovarian follicular development, explaining the numerous immature follicles seen on ultrasound.¹⁵ Androgens also have systemic effects on the development of hirsutism, acne, and central obesity.

Androgens are ultimately converted to estrogen by the peripheral adipose tissue, increasing net estrogen production. Estrogen stimulates proliferation and differentiation of the endometrium which, when unopposed by progesterone, can increase the risk for endometrial hyperplasia and tumorigenesis. Estrogen also inhibits the anterior pituitary gland

Table II. Differential diagnosis of polycystic ovary syndrome

Differential diagnosis	Clinical features	Laboratory evaluation
Pregnancy	Amenorrhea	Elevated serum or urine hCG
Premature ovarian failure	Amenorrhea	Elevated follicle-stimulating hormone, elevated LH, and low-normal estradiol levels
Hypothyroidism	Amenorrhea, fatigue, cold intolerance, constipation, and weight gain	Elevated thyroid-stimulating hormone and low thyroxine levels
Hyperprolactinemia	Amenorrhea and galactorrhea	Elevated prolactin level
Late-onset congenital adrenal hyperplasia	Hyperandrogenism and amenorrhea	Elevated day 5 morning level of 17-hydroxyprogesterone
Virilizing ovarian/adrenal tumor	Amenorrhea, hyperandrogenism, clitoromegaly, deepening of voice, increased muscle mass, and rapidly progressive hirsutism or alopecia	Total testosterone >200 ng/dL, DHEAS >700 µg/dL, and elevated androstenedione
Cushing syndrome	Hyperandrogenism, amenorrhea, hypertension, abdominal striae, truncal obesity, facial plethora, glucose intolerance, pedal edema, and easy bruising	Elevated 24-hr urine free cortisol level, unsuppressed morning serum cortisol during the low-dose dexamethasone suppression test, and elevated midnight salivary cortisol

DHEAS, Dehydroepiandrosterone sulfate; hCG, human chorionic gonadotropin; LH, luteinizing hormone.

Table III. Polycystic ovary syndrome phenotypes based on the 2003 Rotterdam criteria²

Phenotype	Prevalence	Clinical features
Severe PCOS	61%	Irregular menses, polycystic ovaries, hyperandrogenemia, and hyperinsulinemia
Hyperandrogenism and chronic anovulation	7%	Irregular menses, normal ovaries, hyperandrogenemia, and hyperinsulinemia
Ovulatory PCOS	16%	Normal menses, polycystic ovaries, hyperandrogenemia, and hyperinsulinemia
Mild PCOS	16%	Irregular menses, polycystic ovaries, mildly raised androgen levels, and normal insulin levels

PCOS, Polycystic ovary syndrome.

from secreting FSH, which further contributes to preferential LH secretion. Insulin is another hormone involved in the pathogenesis of PCOS. Similar to LH, insulin stimulates the ovarian theca cell to secrete androgens. Insulin also inhibits hepatic production of sex hormone-binding globulin (SHBG), thereby elevating free testosterone. The net result is an increase in androgen levels. Finally, obesity plays an important role in these hormonal pathways by engendering insulin resistance, further stimulating the net production of androgens. Androgen excess contributes toward abdominal obesity, which subsequently propagates the cycle. Weight loss has been shown to effectively halt this cycle, restoring ovulation and decreasing insulin and testosterone levels among women with PCOS.¹⁶⁻¹⁸

CLINICAL FEATURES

Key points

- Hyperandrogenism, oligo- or anovulation, and polycystic ovaries are the hallmark

clinical features of polycystic ovary syndrome; other important features include insulin resistance, obesity, cardiovascular disease, obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric disease

- Cutaneous manifestations of polycystic ovary syndrome include signs of insulin resistance, such as acanthosis nigricans, and signs of hyperandrogenism, such as hirsutism, acne, and hair loss
- Chronic anovulation predisposes patients to infertility and endometrial cancer
- Polycystic ovaries are defined by the presence of ≥ 12 2- to 9-mm diameter follicles in each ovary and/or increased ovarian volume (defined as >10 mL)

PCOS has variable clinical manifestations. The 3 distinguishing features include hyperandrogenism, chronic anovulation, and ultrasonographic evidence of polycystic ovaries. Other important features evident among this population include insulin

Table IV. Multisystem effects of polycystic ovary syndrome

System	Manifestations
Endocrine	Type 2 diabetes mellitus, amenorrhea, and hyperandrogenism
Reproductive	Infertility and endometrial hyperplasia/cancer
Cardiovascular	Coronary artery disease, dyslipidemia, and hypertension
Dermatologic	Hirsutism, acne, alopecia, and acanthosis nigricans
Gastrointestinal	Nonalcoholic steatohepatitis
Pulmonary	Obstructive sleep apnea
Psychiatric	Depression and anxiety

resistance, cardiovascular disease, obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric manifestations (Table IV).

Hyperandrogenism

Hyperandrogenism is one of the most important diagnostic features of PCOS and the most relevant to the role of dermatologists in diagnosis and management of the disorder. Clinical signs include hirsutism, acne, seborrhea, and less commonly hair loss. Any of these signs in addition to the presence of irregular menses should prompt consideration of the diagnosis of PCOS. An initial laboratory work-up includes serum total and free testosterone (calculated is most accurate), SHBG, dehydroepiandrosterone sulfate (DHEAS), prolactin, and a pelvic ultrasound. Other causes of amenorrhea and hyperandrogenism can be ruled out with laboratory tests (Table II). If there is high clinical suspicion for PCOS or another endocrinopathy, referral to an endocrinologist should be considered. Up to two-thirds of women with PCOS will have elevated total testosterone levels, which are associated with greater metabolic and reproductive morbidity.¹⁹ Elevations in free testosterone, however, are felt to be a more sensitive marker of hyperandrogenemia.²

Notably, signs of virilization, such as deepening of the voice, increased muscle mass, and rapidly progressive hirsutism, are rare manifestations of PCOS and should prompt an evaluation for underlying androgen secreting tumors. Signs of androgen excess are most often evident during puberty, but can occur after puberty, especially in the setting of weight gain.

Hirsutism, defined as excessive terminal body hair in a male distribution, often suggests underlying hyperandrogenism. It is frequently seen on the upper lip, chin, areola, chest, back, and lower

abdomen (Fig 1). Up to 60% of women with PCOS have hirsutism.^{20,21} Women with hirsutism have increased follicularly based 5α-reductase activity, which is locally stimulated by androgens, insulin, and insulin-like growth factor.^{22,23} Increased levels of 5α-reductase fosters the conversion of testosterone to dihydrotestosterone, which stimulates hair growth. The degree of hirsutism varies depending on ethnicity; women from South Asia tend to have a higher prevalence while women from Japan have a lower prevalence.²⁴⁻²⁶ Hair follicles appear to have varying sensitivities among different ethnicities, explaining this disparity.^{22,25}

Acne is another common manifestation of hyperandrogenism among women with PCOS. Compared with normal pubertal acne, women with PCOS have predominantly inflammatory lesions on the lower face, neck, chest, and upper aspect of the back. Women with moderate to severe acne should be investigated for PCOS, because 19% to 37% of patients with moderate to severe acne meet the criteria for this disorder.^{27,28} Acne that originates or persists into adulthood and that is refractory to conventional therapies should raise suspicion for underlying PCOS. Ovarian and adrenal androgens, such as androstenedione, testosterone, dehydroepiandrosterone (DHEA), and DHEAS stimulate comedone production by binding to androgen receptors on the pilosebaceous unit, thereby increasing sebaceous gland size, activating sebum production and causing abnormal follicular epithelial cell keratinization.^{22,29} Sebum production leading to *Propionibacterium acnes* overgrowth triggers the pathways that result in inflammatory acne lesions. 5α-reductase plays an active role in the local effects of androgens. The heterogeneity of 5α-reductase enzymes (isoenzymes types 1 and 2) explains the varying dermatologic effects of androgens.²² Isoenzyme type 1 is present in sebaceous glands; type 2 is found in hair follicles. The clinical presentation of women with hyperandrogenism varies depending on the activity of these 2 isoenzymes. Serum levels of androgens do not seem to correlate with degree of hirsutism or acne—the sensitivity of androgen receptors and local levels of androgens play a more significant role.³⁰ This explains why many women with hirsutism and/or acne will not have an underlying endocrinopathy.

Alopecia is another important clinical feature of hyperandrogenism. Androgens stimulate the conversion of terminal follicles to vellus hair and also decrease the percentage of anagen hairs. This is achieved with local elevation of 5α-reductase levels and androgen receptors along with a decrease in



Fig 1. Hirsutism and acne are common dermatologic manifestations of polycystic ovary syndrome.

cytochrome P450, which reduces the conversion of testosterone to estrogen.^{22,31} Among women with PCOS, alopecia is an infrequent finding.³² For this reason, it is important to exclude other common causes of hair loss in women, such as thyroid abnormalities, iron deficiency anemia, alopecia areata, and telogen effluvium. Alopecia among women with PCOS can present with either a typical female pattern, with hair loss predominantly located in the central scalp with preservation of the frontal hairline, or, less commonly, male pattern baldness, with both frontotemporal and vertex recession.^{32,33}

Chronic anovulation and endometrial cancer

PCOS is the leading cause of anovulatory infertility. Chronic anovulation can have pervasive consequences on fertility and oncologic risk. Women present with oligomenorrhea (<9 menses a year) or amenorrhea (missed menses for ≥ 3 months). These aberrant menstrual cycles often appear around the time of menarche, although they can occasionally appear later on in the setting of weight gain. Obese patients with PCOS who lose weight tend to have restoration of their menstrual cycles.^{16,18} The ovaries are stimulated preferentially by LH, which results in ovarian androgen production. Local effects of androgens on the ovary arrest follicular development, preventing ovulation and progression into the luteal phase. In this context, estrogen levels are elevated without cyclical progesterone secretion. Progesterone is necessary to inhibit the proliferation and differentiation of the secretory endometrium. This constant stimulation of the endometrium by estrogen, unopposed by progesterone, increases the risk of endometrial hyperplasia and endometrial adenocarcinoma.³⁴ Other features associated with PCOS, such as hyperinsulinemia, elevated insulin-like growth factor (IGF-1), obesity, and hyperandrogenism also have mitogenic effects on

the endometrium and are independently associated with endometrial cancer.³⁵

Polycystic ovaries

According to the 2003 Rotterdam criteria, polycystic ovaries are 1 of the 3 diagnostic criteria. Polycystic ovaries on ultrasound are defined by the presence of ≥ 12 follicles in each ovary (each follicle measuring 2-9 mm in diameter) and/or an increased ovarian volume of >10 mL (Fig 2). When evaluating adolescent girls, ovarian volume size should be the sole criteria used to evaluate for polycystic ovaries because a transabdominal route is preferred and is less sensitive for the identification of follicles.³⁶ Among the general population of women with regular menstrual cycles and without any criteria for PCOS, 16% to 25% have polycystic ovaries on ultrasound.^{37,38} Polycystic ovaries are found in 92% of women with hirsutism, 87% of women with oligomenorrhea, and 82% of reproductive age women with type 2 diabetes mellitus.^{39,40} Insulin resistance, hyperandrogenism, and changes in SHBG seem to be involved in the development of the polycystic ovarian morphology, even among patients with ovulatory menstrual cycles.⁴¹

Other clinical features

Metabolic complications. PCOS is associated with several metabolic complications, most prominently metabolic syndrome, obesity, and insulin resistance. Up to 47% of women with PCOS have metabolic syndrome.⁴² The diagnostic criteria for metabolic syndrome have been established by the Adult Treatment Panel (ATP) III and include ≥ 3 of the following: waist circumference >88 cm, triglyceride level ≥ 150 mg/dL, high-density lipoprotein cholesterol <50 mg/dL, blood pressure $\geq 130/85$, and fasting glucose level ≥ 100 mg/dL. This close association between PCOS and metabolic syndrome appears to have an even stronger

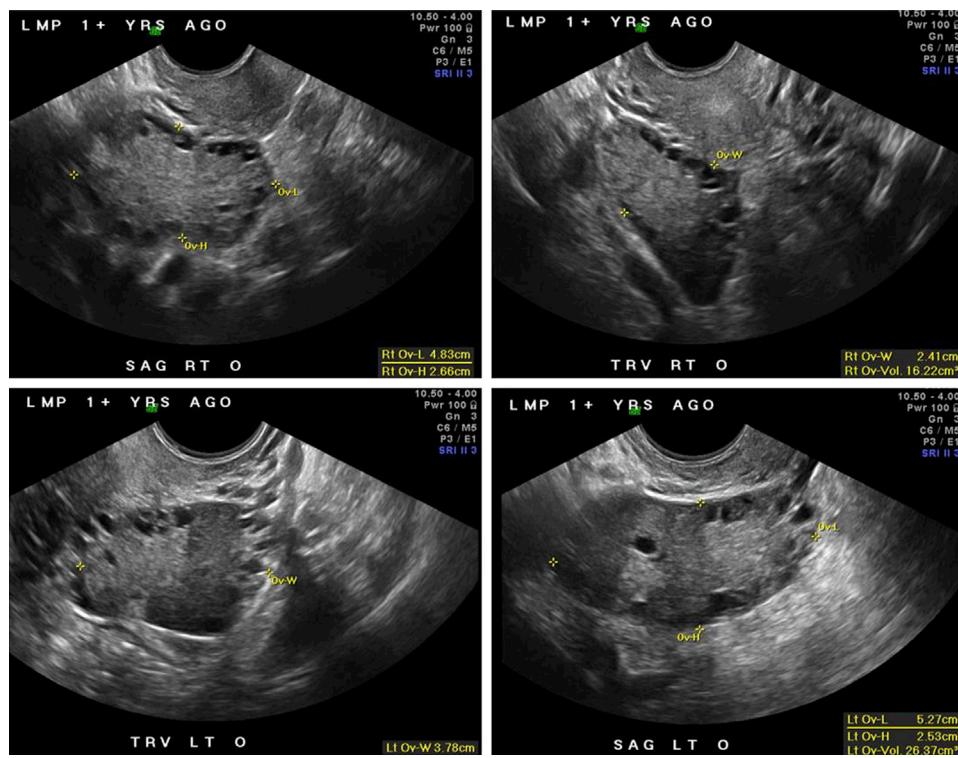


Fig 2. A transvaginal pelvic ultrasound scan reveals bilaterally enlarged ovaries with multiple small follicles of similar size along the periphery, which has a “string of pearls” appearance. The top 2 images show the right ovary (volume, 15 cc) in the sagittal and transverse views. The bottom 2 images show the left ovary (volume, 26 cc) in the sagittal and transverse views.

correlation among black women. Recently, a retrospective cohort study of 519 adolescents and adults with PCOS found a 44% increased risk for metabolic syndrome and cardiovascular disease among black women relative to white women.⁴³

Obesity is present in as many as 75% of women with PCOS,⁴⁴ although this number varies depending on geography and is lower in other countries that have an overall lower prevalence of obesity, such as Finland, Greece, and Spain.⁴⁵⁻⁴⁷ Central obesity appears to play a direct role in the pathophysiology of PCOS by contributing to insulin resistance and increasing androgen levels. In turn, hyperandrogenism and insulin resistance contribute to obesity, which perpetuates the cycle. A metaanalysis comparing obese to overweight women with PCOS revealed that obese women had significantly increased androgen, estrogen, and insulin levels compared to overweight women, further emphasizing the role that obesity has in the clinical picture of PCOS.⁴⁸

Insulin resistance is common among patients with PCOS independent of obesity.⁴⁹ In a prospective controlled trial of 254 women with PCOS, 31% were found to have impaired glucose tolerance, while 7.5% had type 2 diabetes mellitus.⁵⁰ When

examining the nonobese population with PCOS in that same study, the prevalence of impaired glucose tolerance was 10%, while the prevalence of diabetes was 1.5%.⁵⁰ While hyperinsulinemia is not part of the diagnostic criteria for PCOS, insulin plays an essential role in the development of anovulation and hyperandrogenism both by stimulating the theca cells to secrete testosterone and by decreasing the hepatic release of SHBG. This is further supported by the ability of insulin-sensitizing agents, such as metformin and thiazolidinedione, to lower androgen levels and induce ovulation.^{51,52}

The cutaneous signs of hyperinsulinemia include acanthosis nigricans, striae distensae, and acrochordons. Acanthosis nigricans manifests as velvety hyperpigmented thickened plaques predominantly on the nape and sides of the neck, axillae, and groin. Elevated insulin levels bind to IGF-1 receptors, thereby stimulating proliferation of the epidermal keratinocytes and dermal fibroblasts.⁵³ Up to 50% of obese patients with PCOS have acanthosis nigricans, prompting an evaluation for impaired glucose tolerance in this population.⁵⁴

Cardiovascular disease. Women with PCOS have an increased risk of developing cardiovascular disease. However, it is unclear if PCOS is an

independent risk factor for cardiovascular disease or a result of the comorbidities associated with PCOS, such as hypertension,⁵⁵ diabetes,⁵⁵ and dyslipidemia.^{56,57} Patients with PCOS do have increased serum concentrations of cardiovascular disease risk markers, such as C-reactive protein, homocysteine, vascular endothelial growth factor, and plasminogen activator inhibitor-1.⁵⁸ A study examining carotid intima media thickness as a surrogate for coronary artery disease found that patients with PCOS had a larger plaque index, even after controlling for body mass index (BMI), cholesterol level, and blood pressure.⁵⁹ In addition, coronary artery calcification, when measured via electron beam computed tomography, is more prevalent among women with PCOS.⁶⁰ A metaanalysis assessing the risk of coronary heart disease and stroke among patients with PCOS found a 2-fold risk compared to patients without PCOS. When adjusting for BMI, the risk increased by 55%.⁶¹ Despite the compelling evidence, a prospective long-term study comparing women with PCOS to controls over a 20-year period concluded that postmenopausal women with PCOS do not have an increased number of cardiovascular events, despite having a strong cardiovascular risk profile.⁶² However, this Scandinavian population had a smaller waist-to-hip ratio and lower BMI compared with other PCOS populations, which may not be representative of the group as a whole. While the data are controversial as to whether or not PCOS is an independent predictor of cardiovascular events, the consensus is that this population is vulnerable for cardiovascular disease and should be a target for primary prevention. Patients should be closely monitored and managed for obesity, diabetes, hyperlipidemia, and hypertension. The initial evaluation involves a fasting lipid panel, annual blood pressure and BMI calculations, and a 2-hour oral glucose tolerance test every 1 to 2 years.⁶³

Obstructive sleep apnea, nonalcoholic steatohepatitis, and psychiatric manifestations. Patients with PCOS have a 5- to 10-fold higher risk of obstructive sleep apnea (OSA) compared to similarly obese patients without PCOS.⁶⁴ The etiology is in part hormonally mediated. Women with PCOS have decreased levels of progesterone, a hormone that has a protective effect by dilating upper airway muscles and decreasing airway resistance. Conversely, the elevated levels of testosterone among this population increase the apneic threshold. The combination of decreased progesterone levels and increased testosterone levels make the patient with PCOS susceptible for the development of OSA. Interestingly, treatment of OSA with continuous positive airway pressure has been shown to increase insulin sensitivity and decrease

diastolic blood pressure, independent of changes in weight and fat distribution.⁶⁵ The physiology is thought to be driven by reductions in both norepinephrine levels and cardiac sympathetic activity.^{58,66}

PCOS is also independently associated with nonalcoholic steatohepatitis. A study comparing women with PCOS to matched controls found that 44% compared to 20% had histologic nonalcoholic steatohepatitis after a liver biopsy specimen had been obtained, even after controlling for diabetes, obesity, and age.⁶⁷

The psychological impact of obesity, infertility, hirsutism, and acne among women with PCOS is a source of recent interest. Women with PCOS have higher rates of depression, anxiety, and eating disorders.^{68,69} Approximately 10% of women with PCOS suffer from these psychological conditions.⁶⁸ Changes in physical appearance, such as hirsutism and obesity, seem to play the greatest role in the psychosocial manifestations.⁷⁰

In conclusion, PCOS is an increasingly common endocrinopathy. The pathophysiology represents a network of interconnecting hormonal pathways with the net result of elevated levels of androgens, insulin, and LH. These aberrant hormones have long-term metabolic, cardiovascular, oncologic, and reproductive implications. Dermatologists should be aware of the clinical features of PCOS and watch for the dermatologic findings of hyperandrogenism and insulin resistance, because these can often be the presenting manifestations of PCOS. Dermatologists are in a key position to make an early diagnosis of the syndrome and to ensure that the overall health risks of these patients are addressed.

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Polycystic ovary syndrome: A review for dermatologists

Part II. Treatment

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Learning Objectives:

After completing this learning activity, participants should be able to describe the range of treatment options for the hyperandrogenic manifestations of polycystic ovary syndrome (PCOS), acne, hirsutism, and androgenetic alopecia, and demonstrate an understanding of the safety and efficacy of the pharmacologic treatments

used for PCOS, including topical therapies, combined oral contraceptive pills, antiandrogen drugs, and insulin-sensitizing drugs.

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Dermatologists are in a key position to treat the manifestations of polycystic ovary syndrome (PCOS). The management of PCOS should be tailored to each woman's specific goals, reproductive interests, and particular constellation of symptoms. Therefore, a multidisciplinary approach is recommended. In part II of this continuing medical education article, we present the available safety and efficacy data regarding treatments for women with acne, hirsutism, and androgenetic alopecia. Therapies discussed include lifestyle modification, topical therapies, combined oral contraceptives, antiandrogen agents, and insulin-sensitizing drugs. Treatment recommendations are made based on the current available evidence. (J Am Acad Dermatol 2014;71:859.e1-15.)

Key words: acne; androgenetic alopecia; combined oral contraceptive pills; cyproterone acetate; drospirenone; hirsutism; insulin-sensitizing drugs; polycystic ovary syndrome; spironolactone.

Although patients with polycystic ovary syndrome (PCOS) often present to dermatologists with cutaneous concerns, it is essential to provide education regarding the metabolic and fertility-related implications of PCOS and to form a multidisciplinary team that includes a primary care physician and an endocrinologist. Understanding patients' reproductive goals and medical health allows providers to develop a comprehensive medical plan. The decision to begin pharmacologic treatment for dermatologic manifestations of PCOS must be tailored to each woman's specific concerns.

Pharmacologic treatment is not necessary for all patients with PCOS, and mild forms of hirsutism, acne, and androgenetic alopecia may be satisfactorily managed with standard nonhormonal agents (Table I) that—aside from laser hair removal, minoxidil, and eflornithine—will not be reviewed here.¹⁻⁴ In addition, a discussion of weight loss, diet, and exercise in obese patients may be helpful in managing cutaneous symptoms. This review focuses primarily on pharmacologic management of PCOS, because many patients find standard topical agents ineffective and are eager to target the hormonal cause underlying their dermatologic concerns.

NONHORMONAL TREATMENTS

Key points

- Changes in diet and exercise leading to weight loss improves fertility and metabolic findings, but studies conflict regarding efficacy on hirsutism and acne
- Topical nonhormonal therapies and laser hair removal may be effective for acne, hirsutism, and androgenetic alopecia in the

Abbreviations used:

cOCP:	combined oral contraceptive pill
CPA:	cyproterone acetate
EE:	ethinyl estradiol
FDA:	US Food and Drug Administration
FG:	Ferriman-Gallwey
ISD:	insulin-sensitizing drug
PCOS:	polycystic ovary syndrome
SHBG:	sex hormone binding globulin
TZD:	thiazolidinedione
VTE:	venous thromboembolism

PCOS population and are useful first-line agents

Lifestyle changes

Lifestyle changes are often recommended as first-line treatment for PCOS to benefit overall health. Studies examining dietary interventions show conflicting effects on hirsutism, likely influenced by type of restrictive diet and study length, because studies often span weeks to months, which is not long enough to observe biologic changes on dermatologic effects. A study in 78 women found that of those who lost >5% body weight after 4 weeks of a calorie-restricted diet, 30% experienced improvement in hirsutism as measured using the Ferriman-Gallwey (FG) score (Fig 1); the other 70% of patients did not report improvement.⁵ Other studies have also shown improvements in hirsutism with caloric restriction after 6 months.⁶ However, a Cochrane review of 3 randomized, controlled trials concluded that there is no improvement in hirsutism after dietary changes.⁷⁻⁹ In addition, there are insufficient data to suggest that lifestyle changes play a role in PCOS acne management.¹⁰ However,

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Table I. Treatments for polycystic ovary syndrome

Lifestyle
Weight loss
Exercise
Glucose control
Hormonal
Combination estrogen and progesterone oral contraceptives
Antiandrogen: spironolactone, cyproterone acetate, drospirenone, and flutamide
Inhibition of peripheral androgen conversion: finasteride (5α -reductase inhibitors)
Insulin-sensitizing agents
Metformin
Thiazolidinediones
Nonhormonal
Acne: standard acne therapy, including topical retinoids, topical and oral antibiotics, benzoyl peroxide, topical dapson, peels, and isotretinoin
Hirsutism: bleaching, shaving, waxing, electrolysis, laser hair removal, and eflornithine
Androgenetic alopecia: minoxidil

for other aspects of PCOS, such as weight and adiposity distribution, insulin resistance, and fertility, weight loss can be helpful.^{10,11} Therefore, while additional research is needed, we continue to encourage lifestyle changes in PCOS patients.

Topical therapies

Topical therapies represent a safe starting point of treatment for androgenetic alopecia and hirsutism given their safety profiles. However, there have been no studies to date of minoxidil or eflornithine use specifically in PCOS.

Laser hair removal. Laser hair removal is a mainstay of treatment for hirsutism, but few studies exist in the PCOS population, and the limited data available conflicts regarding whether laser hair removal is as effective in patients with PCOS compared to those without.¹²⁻¹⁴ However, all studies agree that laser hair removal is helpful and can reduce emotional burden and increase the quality of life of PCOS patients affected by hirsutism.¹³ It should be noted that laser hair removal is ineffective on nonpigmented hairs, and potential side effects include pain, swelling, redness, and postinflammatory hyperpigmentation. Certain lasers are not advisable for use in patients with darker Fitzpatrick skin types. Laser hair removed is not often covered by insurance.¹⁵

Aside from a small study in 52 PCOS patients where metformin in addition to intense pulsed-light therapy significantly decreased hair count, laser hair removal has not been studied in conjunction with

medical therapies.¹⁶ Although it has been hypothesized that hormonal agents used concurrently with laser hair removal may maximize permanent laser hair removal by preventing chronic hair terminalization in patients with PCOS, this has not been studied.¹⁴

Minoxidil. Minoxidil is thought to promote hair growth via vasodilatation, enhanced cell proliferation and DNA synthesis, and increased angiogenesis.^{17,18} Two concentrations of minoxidil (2% and 5%) are approved by the US Food and Drug Administration (FDA) for use in men, but only 2% is approved by the FDA for use in women. In 381 women treated twice daily for 48 weeks, 5% minoxidil was superior to placebo and increased hair growth by 24.5 hairs/cm² compared to 20.7 hairs/cm² with 2% minoxidil, although the difference was not statistically significant.¹⁹ A single-blind study demonstrated equivalent efficacy between minoxidil 5% foam once daily and 2% solution twice daily in women.²⁰ Other studies exploring combined oral contraceptive pills (cOCPs)/minoxidil combination treatments have inconclusive results.²¹

Eflornithine hydrochloride cream. Eflornithine hydrochloride 13.9% cream slows hair growth by irreversible inhibition of ornithine decarboxylase, an enzyme that is necessary in hair follicle assembly.^{22,23} Adverse effects include stinging, burning, and tingling.²⁴ Large randomized, controlled trials have shown statistically significant reductions in both hair length and mass with eflornithine treatment. A study of 594 women found a 23% reduction in hair length and a 26% reduction of hair mass.²⁴ One small randomized trial found a statistically significant difference in hair removal between eflornithine plus laser compared to laser alone.²⁵

COMBINATION ORAL CONTRACEPTIVES WITH PROGESTINS DERIVED FROM 19-NORTESTOSTERONE

Key points

- Combined oral contraceptive pills (ethynodiol diacetate and a synthetic progestin) are the mainstay of therapy for patients with polycystic ovary syndrome
- Combined oral contraceptive pills differ in progestin androgenic activity and progestin dose. However, all combined oral contraceptive pills are antiandrogenic by virtue of ethynodiol diacetate

Mechanisms of action

cOCPs are the first-line pharmacologic therapy for PCOS patients who are not trying to conceive.^{26,27} cOCPs are useful for contraception and effective

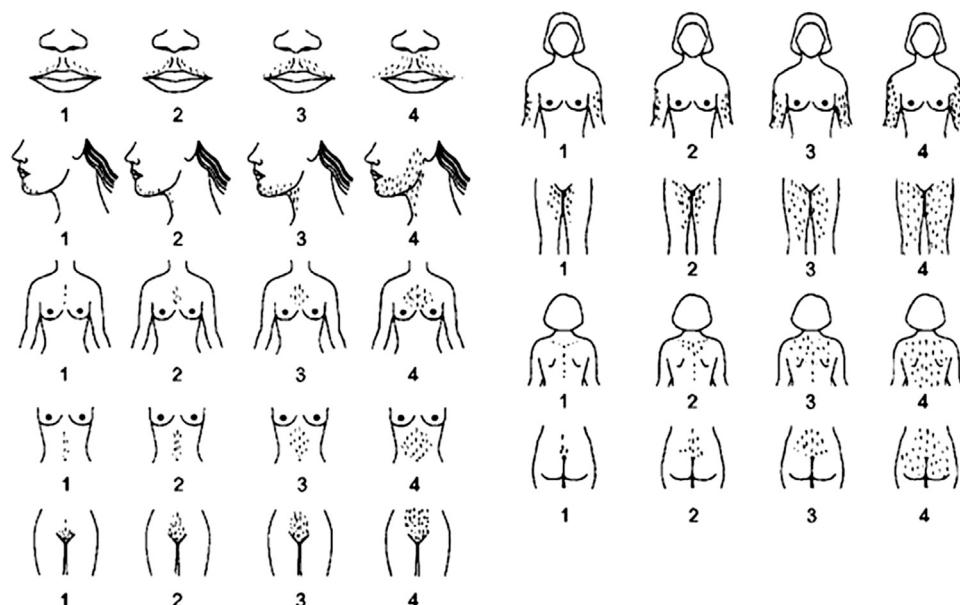


Fig 1. Modified Ferriman-Galwey scoring system. Nine body areas (ie, the upper lip, chin, chest, arm, upper abdomen, lower abdomen, upper aspect of the back, lower aspect of the back, and thighs) are scored as follows: 1 point (minimal terminal hairs), 2 points (hair growth is more than minimal but not yet that of a man), 3 points (hair growth is of a man who is not very hairy), and 4 points (equivalent to a hairy man). If no terminal hairs are present in the body area, the score is 0. Terminal hairs are typically longer than 0.5 cm and are usually pigmented. (Reprinted with permission from Yildiz et al,¹⁹¹ figure 2, p 57, by permission of the Oxford University Press and from Dr R. Azziz.)

against menstrual irregularities and endometrial hyperplasia. cOCPs contain a low-dose ethinyl estradiol (EE) and synthetic progestin, the majority derived from 19-nortestosterone (Fig 2). Progestins derived from 19-nortestosterone differ from the progestins drospirenone and cyproterone acetate (CPA), which are unrelated to testosterone and antagonize the androgen receptor. These will be discussed separately. Generic equivalents are available for most cOCPs.

cOCPs function as antiandrogens in PCOS via 3 mechanisms. First, estrogen increases hepatic production of sex hormone binding globulin (SHBG), thereby decreasing circulating free testosterone levels. Second, progestin suppression of luteinizing hormone secretion decreases ovarian androgen production. Third, progestins compete to differing extents for 5 α -reductase and the androgen receptor.²⁷⁻²⁹ All cOCPs may be thought of as having a net suppressive effect on androgens, largely because of the action of estrogen on SHBG.³⁰ However, older 19-nortestosterone-derived progestins, including levonorgestrel, norgestrel, and norethindrone, may have more androgenic activity as measured by effects on SHBG and free testosterone. In contrast, newer 19-nortestosterone-derived progestins, specifically

norgestimate, desogestrel, and gestodene, have less androgenic activity and do not significantly lower SHBG.^{31,32} Androgenicity of progestins is dependent on both type and dosage; 2 cOCPs with the same progestin may have different androgenic activity based on estrogen doses and/or progestin. However, the clinical relevance of these differences on cutaneous features of PCOS is unclear.³³

Many factors enter into the selection of a contraceptive method, including personal and family history, concurrent medications, and previous adverse effects of cOCPs such as breakthrough bleeding, headaches, nausea, breast tenderness, mood disturbances, and sexual side effects. cOCPs are contraindicated in smokers, patients with migraines, patients with history of stroke or hypertension, and patients with personal or family history of thromboembolism, liver disease, or diabetes. When selecting contraception, these factors must be weighed in conjunction with cutaneous effects.^{34,35}

Hirsutism

cOCPs have long been used to treat hirsutism but are approved by the FDA for this indication.³⁶⁻⁴⁰ In pooled data, cOCPs were more effective than placebo in 34 women, with a mean FG score reduction

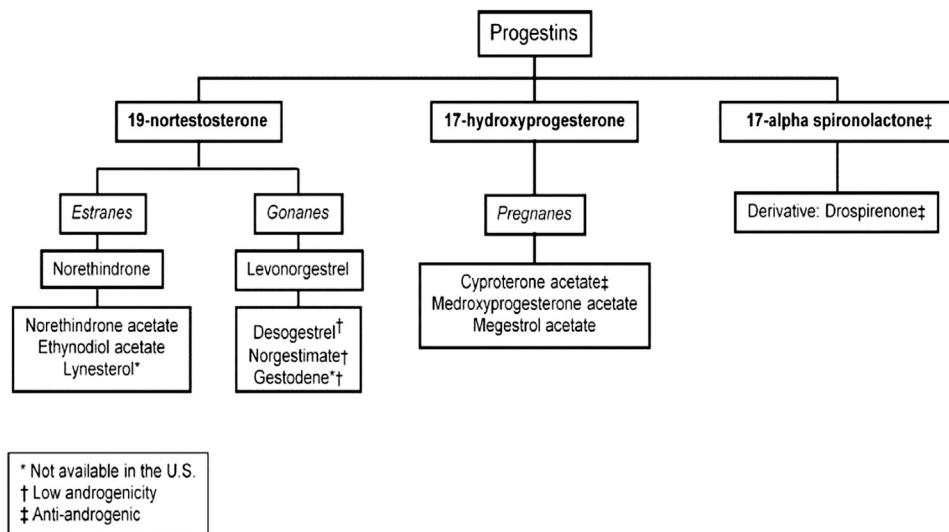


Fig 2. Classification of commonly used progestins. Adapted from Carr,³¹ Grimes,¹⁹² and Sitruk-Ware.^{193,194}

of 8.^{1,41,42} In 1 representative study, PCOS patients treated with desogestrel 15 µg/EE 30 µg had a FG score reduction from 16 to 8 over the first 9 months, with no significant decline after month 9.⁴³

Limited data comparing older versus newer progestins have not shown differences in hirsutism effects. The study above found no difference in patients treated with desogestrel/EE and CPA 2 mg/EE 35 µg, an antiandrogenic cOCP.⁴³ Similarly, another study in hirsute women reported that desogestrel/EE was as effective as levonorgestrel 15 µg/EE 30 µg; free testosterone dropped significantly in the desogestrel group.^{44,45}

Acne

cOCPs are typically effective for acne, but data for newer progestins are limited. In a Cochrane metaanalysis, cOCPs reduced inflammatory and noninflammatory facial lesion counts, severity grades, and self-assessed acne scores in 9 trials as compared with placebo.⁴⁶ However, data regarding cOCP differences in efficacy is difficult to interpret. In 4 trials comparing the older progestin levonorgestrel with the newer progestin desogestrel, 2 studies found no difference and 2 favored desogestrel—the latter including the largest study to date ($n = 788$) that also used a lower dose of EE.⁴⁷⁻⁵⁰ A smaller study confirmed acne reduction,⁵¹ and a review of cOCP effects on acne reported an inflammatory count decrease of 30% to 60% and symptom improvement in 50% to 90% of PCOS patients.⁵² cOCP formulations that are approved by the FDA for acne include graduated EE with constant norethindrone acetate and norgestimate/EE preparations.

Metabolic factors

Although cOCPs are widely considered first-line therapy in PCOS, their use is controversial given the potential side effects. In addition to increasing risk of thromboembolism, stroke, myocardial infarction, and breast cancer, they may also increase insulin resistance, plasma lipids, and cardiac risk^{27,53}; metabolic side effects may be greater with more androgenic progestins.⁵⁴⁻⁵⁶ The current recommendations suggest low-dose cOCPs (<50 µg EE) to decrease cOCP-related diabetes risk. cOCPs also decrease low- and high-density lipoprotein and total cholesterol, but increase triglycerides, and should be avoided in women with hypertriglyceridemia.⁵⁷ Each patient's cardiometabolic risk profile should be evaluated before beginning therapy with cOCPs.²⁷ The addition of metformin may be useful in offsetting insulin resistance.⁵⁸

COMBINED ORAL CONTRACEPTIVE PILLS WITH ANTIANDROGEN PROGESTINS

Key points

- **Antiandrogen progestin combined oral contraceptive pills include cyproterone acetate and drospirenone**
- **Drospirenone-containing combined oral contraceptive pills may increase risk of thromboembolism**
- **Careful consideration of cardiovascular risk factors, including age, should be given before prescribing drospirenone-containing combined oral contraceptive pills**

Cyproterone acetate

CPA 2 mg/EE 35 µg is used in Europe and Canada but is not approved by the FDA for use in the

United States. It is a steroidal antiandrogen (a 17-hydroxyprogesterone derivative) that competes with dihydrotestosterone for androgen receptor binding, inhibiting 5 α -reductase activity. It also results in diminished testosterone and androstenedione production via negative feedback on the hypothalamic-pituitary axis and inhibiting luteinizing hormone secretion.⁵⁹ It has been extensively studied for both acne and hirsutism.

Drospirenone

Drospirenone has both anti-androgen and mineralocorticoid properties. Derived from spironolactone, drospirenone is available in the United States as drospirenone 3 mg/EE 30 μ g, drospirenone 3 mg/EE 20 μ g, and drospirenone 3 mg/EE 20 μ g plus levomefolate calcium 451 μ g. Drospirenone treats hyperandrogenism by blocking ovarian steroid production, reducing adrenal androgen synthesis and blocking peripheral androgen receptors in the dermis and pilosebaceous units.⁴⁰ Both drospirenone 3 mg/EE 20 μ g and drospirenone 3 mg/EE 20 μ g plus levomefolate calcium 451 μ g are approved by the FDA for the treatment of moderate acne.

Only drospirenone/EE 20 μ g and drospirenone/EE 20 μ g plus levomefolate calcium 451 μ g are approved by the FDA for the treatment of acne and premenstrual dysphoric disorder. Drospirenone/EE 30 μ g is currently available in a generic version, which may be a financial consideration.

Risk of thromboembolism with combined oral contraceptive pills containing drospirenone and other progestins

It is well known that cOCPs increase venous thromboembolus (VTE) and pulmonary embolism risk, depending on type of progestin and dose of EE in the cOCP.⁶⁰ Relative to nonusers, levonorgestrel increases VTE risk 3.6-fold, gestodene 5.6-fold, desogestrel 7.3-fold, CPA 6.8-fold, and drospirenone 6.3-fold.⁶¹ Observational studies report a 1- to 3-fold VTE increase when comparing drospirenone to levonorgestrel-containing cOCPs.⁶¹⁻⁷² VTE often occurs in patients >35 years of age with at least 1 risk factor for thrombotic disease during the first year of treatment.^{61,62,73,74} Although there is a known dose-response relationship between EE dosage and VTE events with cOCPs, especially with EE >50 μ g,⁷⁵ recent studies in drospirenone-containing cOCPs suggest either no difference between EE 20 μ g and 30 μ g,⁶² or even elevated risk with EE 20 μ g compared with 30 μ g.⁷⁶ There has been significant recent media discussion

regarding VTE events in conjunction with drospirenone use. In April 2012, the FDA concluded that drospirenone-containing birth control pills may be associated with a higher risk for blood clots compared to other progestin-containing pills and added this information to package labels.⁷⁷

However, absolute VTE risk of drospirenone-containing cOCPs (23-137 events/100,000 woman-years) is not much more than traditional levonorgestrel-containing cOCPs (6-92 events/100,000 woman-years), and comparatively, risk in pregnancy is much higher than both (<290 events/100,000 woman-years).^{78,79} In PCOS patients with increased cardiovascular risk factors, it is important to weigh the risk:benefit ratio. In patients with additional risk factors, different medications should be explored. However, with careful consideration, providers can safely prescribe drospirenone-containing cOCPs.

Hirsutism

Small studies suggest that CPA is effective in PCOS for treating hirsutism and superior to placebo, desogestrel/EE, and drospirenone.^{42,80-82} A Cochrane review determined that CPA improves hirsutism subjectively when compared to placebo, but is not more effective than ketoconazole, spironolactone, flutamide, finasteride, or gonadotropin-releasing hormone analogues.⁵⁹

Although not approved by the FDA for the treatment of hirsutism, drospirenone may be highly effective. In 1 prospective study with 30 of 48 PCOS patients, drospirenone/EE 30 μ g showed a mean decrease in FG score of 67% and 78% after 6 and 12 months, respectively, with the greatest improvement on the chest and abdomen, followed by the upper lip and chin.⁴⁰ Another study in PCOS found a 33% relative decrease in hirsutism when comparing drospirenone/EE 30 μ g with desogestrel/EE, even 6 months after treatment discontinuation.⁸³

Acne

Antiandrogen cOCPs are also effective for acne. Comparisons of CPA with dienogest 2 mg/EE 30 μ g,⁷⁹ norgestimate 180 to 215 μ g/EE 35 μ g,⁸⁰ and drospirenone/EE 30 μ g⁸⁴ have shown no significant differences.^{46,85,86} Drospirenone/EE 30 or 20 μ g may both be effective in treating acne in women with and without PCOS as compared with placebo.⁸⁷⁻⁹⁰ One large randomized study showed a greater mean percentage change in total lesion count after 6 months of drospirenone/EE 30 μ g compared to triphasic norgestimate 0.18/0.215/0.250 mg/EE 35 μ g.^{46,91}

NONORAL CONTRACEPTIVE ANTIANDROGENS: SPIRONOLACTONE, FINASTERIDE, AND FLUTAMIDE

Key points

- Antiandrogen medications are helpful in treating hirsutism, with no clear difference in efficacy among agents
- All antiandrogens are harmful during pregnancy, and concomitant contraception must be emphasized with patients
- No antiandrogens are approved by the FDA for the treatment of acne or hirsutism

Spirotonolactone

The aldosterone antagonist spironolactone shows dose-dependent competitive inhibition of the androgen receptor and inhibits 5 α -reductase.^{1,92} Of note, drospirenone 3 mg is approximately equivalent to CPA 1 mg and spironolactone 25 mg.⁹³ An 8-year study on spironolactone safety reported no serious complications; rare side effects include hyperkalemia, increased with adrenal, liver, or kidney disease.⁹⁴ Other side effects include menstrual irregularity (minimized by concurrent cOCP use), breast tenderness, and headaches. A recent cohort study found no increased risk of breast cancer with spironolactone.^{94,95}

Finasteride

Finasteride is a progesterone-derived 5 α -reductase inhibitor that blocks the conversion of testosterone to the potent androgen dihydrotestosterone.⁹⁶ The most commonly used dose is 5 mg per day, although studies suggest equal efficacy with 2.5 mg per day.⁹⁷ Common side effects include dry skin, libido reduction, and headaches.⁹⁸

Flutamide

Flutamide is a potent nonsteroidal androgen antagonist used in prostate cancer treatment. The recommended dosing is 250 mg per day,⁹⁹ however, lower doses (125 or 62.5 mg/day) may have similar effects with fewer side effects.^{100,101} Flutamide is rarely used because of its hepatotoxicity and high cost, although low doses (250 mg/day) may not be toxic in young and nonobese PCOS patients.¹⁰²

All antiandrogenic agents may be harmful during pregnancy (spironolactone is pregnancy class C, finasteride class X, and flutamide class D). Therefore, we recommend concurrent contraception, when possible a cOCP.

Hirsutism

A metaanalysis comparing antiandrogens in hirsute women, some with PCOS, found all treatment

groups had significantly lower hirsutism scores compared with placebo.^{99,103-107} Studies suggest that antiandrogens alone, spironolactone/cOCP, metformin/cOCP, or flutamide/metformin combinations are all superior to cOCPs or metformin monotherapy.¹⁰⁸⁻¹¹⁰ A representative trial in 40 women, 21 with PCOS, comparing 6 months of spironolactone 100 mg per day, flutamide, or finasteride with placebo had a 40% FG score decrease in all treatment groups.⁹⁹

Spironolactone is most commonly used for hirsutism in PCOS; studies have shown its efficacy specifically in this population.^{111,112} A study exploring appropriate dosing found no difference between 100 and 200 mg per day.¹¹³ Lower doses of spironolactone (25-50 mg/day) in combination with other therapies have also been efficacious in PCOS.^{108,109}

Flutamide 250 mg twice daily may be more effective than finasteride when treating hirsutism in PCOS.^{98,114} When added to a triphasic cOCP, flutamide may also be more effective for hirsutism and acne than cOCP/spironolactone 100 mg per day.¹¹⁵

Acne

Although a Cochrane review found that sample sizes were too small to determine spironolactone efficacy in treating acne,¹¹³ studies have shown improvement with spironolactone 50 to 200 mg per day—but no studies have been conducted on women with PCOS.¹¹⁶⁻¹¹⁹ In 85 patients, spironolactone 50 to 100 mg per day for 24 months demonstrated complete acne clearance in 33%, marked improvement in 33%, and partial improvement in 27%. Patients were undergoing spironolactone monotherapy or combination therapy with cOCPs, antibiotics, or both; subgroup analysis did not find a significant difference in any group.¹¹⁸ In 27 patients, the addition of spironolactone 100 mg per day to drospirenone/EE 30 μ g patients was efficacious, safe, and well tolerated.¹²⁰ Combination flutamide/cOCP improved acne by 80%, whereas spironolactone/cOCP improved acne by 50%.¹¹⁵

Alopecia

Antiandrogens have also been used to treat female pattern hair loss, although not studied specifically in PCOS. Spironolactone, finasteride, and CPA may have beneficial effects.^{21,121-125} In 80 women treated with spironolactone 200 mg and CPA 50 or 100 mg per day, 44% experienced hair regrowth, measured by a visual clinical grading score. Results were not related to hormonal or menopausal status.¹²²

INSULIN-SENSITIZING DRUGS

Key points

- Because insulin-sensitizing drugs improve peripheral insulin sensitivity and decrease androgen production, they are often used as long-term treatment options for patients with polycystic ovary syndrome
- Metformin is the most widely used insulin-sensitizing drug, with the literature suggesting that it improves hirsutism, acne, and acanthosis nigricans
- Metformin may be more efficacious than antiandrogens for hirsutism, but comparisons to combined oral contraceptive pills are inconsistent
- The 2 thiazolidinediones available in the United States, rosiglitazone and pioglitazone, have improved hirsutism and acne in some studies, but have limited use because of cardiovascular side effects

Metformin

Metformin increases peripheral glucose uptake, reduces intestinal glucose absorption, and is the most extensively studied insulin-sensitizing drug (ISD) for patients with PCOS.¹²⁶⁻¹²⁹ However, because of its gastrointestinal side effects, it is not well tolerated and is often used second-line after spironolactone and is best reserved for patients with glucose intolerance, insulin resistance, or who are trying to conceive.

Many studies have explored metformin's effects in PCOS. With regard to hirsutism, several studies have noted FG score decreases with metformin compared with placebo,¹³⁰⁻¹³⁸ while others have not.^{127,139-147} Studies of metformin compared to or combined with cOCPs,^{143,148-151} CPA,^{134,152-154} and flutamide^{7,143,147,148,155,156} are inconsistent. Metformin has been shown to be less effective than both flutamide and spironolactone in the treatment of hirsutism; however, the addition of flutamide was more effective than metformin alone.^{107,148,157,158} A year-long comparison found a 25% FG score reduction with metformin compared with a 5% reduction with CPA^{134,152}; however, in other studies, CPA decreased hirsutism more than metformin.^{153,154}

Data for metformin regarding acne, androgenic alopecia, and acanthosis nigricans in patients with PCOS are inconsistent. Several trials have shown that metformin slightly improves acne in patients with PCOS^{132,134,150,159}; others show that metformin is not effective for acne or androgenic alopecia.^{126,134} In 1 study, 6 months of metformin reduced acanthosis nigricans but only minimally affected hirsutism and acne,^{55,160} while another reported no impact on acanthosis nigricans.^{147,161}

Thiazolidinediones

Thiazolidinediones (TZDs) suppress gluconeogenesis by increasing peripheral glucose uptake and decreasing hepatic glucose production.^{129,162} Troglitazone was effective for hirsutism in patients with PCOS, but is no longer available because of hepatotoxicity.^{148,155,156,163-165} Pioglitazone and rosiglitazone have different side effect profiles, but both have associated cardiovascular risks (rosiglitazone more) and hepatotoxicity.^{127,166-168} They carry a black box warning for increased congestive heart failure risk and nonfatal myocardial infarction. In patients with PCOS who already have an increased cardiac risk, TZDs are second-line to metformin.

In PCOS, studies have shown that rosiglitazone and pioglitazone significantly decreased FG scores,^{128,136,162,169-179} while others reported that neither medication improved hirsutism.^{163,180-182}

TREATMENT RECOMMENDATIONS

Hirsutism

Data suggest that conventional cOCPs have fairly equivalent efficacy for hirsutism. We recommend first-line treatment with cOCPs containing low or antiandrogenic progestins, with appropriate consideration of small increased cardiometabolic risks of androgenic progestins (level of evidence IB; Table II). Data support the efficacy of drospirenone/EE 30 µg for hirsutism.^{40,83} Trials show an effect on hirsutism beginning at 6 months; accordingly, we recommend 6 months of therapy before regimen modification.^{1,183} Next, we recommend the addition of spironolactone when appropriate (level of evidence IA), beginning at 50 mg per day and increasing as needed, keeping in mind that drospirenone therapy accounts for 25 mg of spironolactone when the 2 medications are used together. cOCPs should be prescribed with spironolactone, whenever possible, to avoid teratogenicity and menstrual irregularities. We recommend checking the baseline potassium level, repeated after 1 month and after dose increases (level of evidence IV). We also suggest monitoring blood pressure while the patient is undergoing spironolactone therapy and checking for signs of hypotension, such as dizziness. Spironolactone should be avoided with angiotensin-converting enzyme inhibitors, high-dose nonsteroidal antiinflammatory drugs, or high potassium intake. If drospirenone-containing cOCPs are not prescribed because of a concern for VTE, spironolactone may be used with any cOCP for antiandrogen activity. We currently do not recommend flutamide or finasteride before spironolactone therapy.^{99,115,184}

Table II. Treatment recommendations for the cutaneous manifestations of polycystic ovary syndrome

Cutaneous manifestation of PCOS	Treatment (level of evidence*)
Hirsutism	Lifestyle changes (III) Laser hair removal (IB) Minoxidil 1% or 5% (IB) Eflofene hydrochloride 13.9% (IB) cOCPs containing low- or antiandrogenic progestins (IB) Addition of spironolactone (IA) Other antiandrogens: finasteride and flutamide (IA) Metformin (IB) Thiazolidinediones: pioglitazone and rosiglitazone (IB)
Acne [†]	Lifestyle changes (IV) cOCP containing low- or antiandrogenic progestins (IA) Addition of spironolactone (IB) Other antiandrogens: flutamide (IB) Metformin (III)
Alopecia	Antiandrogens: spironolactone and CPA (IIB) Antiandrogens: finasteride (III)

cOCP, Combined oral contraceptive pill; CPA, cyproterone acetate; PCOS, polycystic ovary syndrome.

*Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from at least 1 randomized controlled trial; level IIB evidence includes evidence from at least 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies; level IV evidence includes evidence from opinions or clinical experience of respected authorities.

[†]After failing topical therapies.

Unfortunately, therapy withdrawal leads to hirsutism relapse. A study comparing spironolactone, desogestrel/EE, flutamide, and CPA reported that patients experienced mean FG score increases of 14.4 with no significant differences between groups 1 year after withdrawal.¹⁸⁵

Acne

In patients who fail to respond to topical therapies, we recommend cOCPs with either low androgenicity or antiandrogenic properties as first-line therapy (level of evidence IA) over oral antibiotic therapy. With concurrent metabolic or cardiovascular risk factors, such as hypertension or elevated thromboembolism risk, we recommend working with the patient's internist or gynecologist to find the optimal cOCP that improves hyperandrogenism symptoms without negatively impacting cardiovascular risk.⁵⁷ There are currently no routine follow-up screening guidelines.¹⁸³

After 3 months of insufficient treatment with a cOCP, we recommend the addition of spironolactone (level of evidence IB) starting at 50 mg per day. Small studies have shown 100 mg per day spironolactone is as effective as 200 mg per day and causes fewer side effects. Flutamide and finasteride data are insufficient to recommend their use.¹¹⁵

We do offer oral antibiotics as second-line therapy for short-term management and as adjunctive treatment when hormonal therapies alone are insufficient. Although there are no data comparing hormonal agents with oral antibiotic medications in patients with PCOS, 1 prospective study found isotretinoin effective in patients with PCOS; however, the relapse rate may have been slightly higher at 2 years posttherapy compared to patients without PCOS.¹⁸⁶ In patients whose acne is severe and refractory to oral antibiotics, oral contraceptives, and spironolactone, isotretinoin use should be considered.

In conclusion, given the absence of consistent evidence regarding the benefits of ISDs on acne or hirsutism, the literature weakly recommends metformin and TZDs.^{96,145,152,176,187-190} Although metformin efficacy remains to be proven, it is safe; the efficacy and safety of TZDs remain questionable.^{180,187} As a result, we typically do not use TZDs. Metformin, however, is useful in patients with glucose intolerance, insulin resistance, or who are trying to conceive; gastrointestinal side effects place it second-line to spironolactone. More longitudinal studies involving larger sample sizes, improved precision, and more aggressive investigations into treatment options are needed, including polytherapies where ISDs are coadministered with antiandrogen medications and/or cOCPs.

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Diet in dermatology

Part I. Atopic dermatitis, acne, and nonmelanoma skin cancer

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After completing this learning activity, participants should be able to describe the relationship between diet and the following conditions: acne, psoriasis, and urticaria.

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Patients commonly inquire about dietary modifications as a means to prevent or manage skin disease. Answering these questions is often challenging, given the vast and conflicting evidence that exists on this topic. This 2-part continuing medical education article summarizes the evidence to date to enable physicians to answer patients' questions in an evidence-based manner. Part I includes atopic dermatitis, acne, and nonmelanoma skin cancer. The role of dietary supplementation, dietary exclusion, food allergy, maternal diet, and breastfeeding in the development and/or prevention of atopic dermatitis is summarized. The dermatoendocrinologic mechanism for the effects of glycemic index/glycemic load and milk on acne is described, as well as related clinical evidence for dietary modifications. Finally, evidence and recommendations for restriction or supplementation of dietary factors in the prevention of nonmelanoma skin cancer, including fat, vitamins A, C, D, and E, and selenium, are reported. (*J Am Acad Dermatol* 2014;71:1039.e1-12.)

Key words: acne; atopic dermatitis; basal cell carcinoma; diet; nonmelanoma skin cancer; nutrition; squamous cell carcinoma.

The role of diet in dermatology is a frequent source of patient inquiry and physician uncertainty. In part I of this continuing medical education article, we discuss the effect of diet on atopic dermatitis (AD), acne, and nonmelanoma skin cancer (NMSC).

ATOPIC DERMATITIS

Key points

- Prenatal followed by postnatal probiotic supplementation decreases the risk of atopic dermatitis
- Postnatal prebiotic supplementation decreases the risk of atopic dermatitis
- Elimination diets are only appropriate for patients who have a food allergy that has been proven by oral food challenge
- Maternal allergen avoidance diets do not prevent atopic dermatitis
- Exclusive breastfeeding and supplementation with hydrolyzed formula is protective against atopic dermatitis for high-risk infants
- For infants at normal risk, breastfeeding is not protective for atopic dermatitis

Seven recent Cochrane Reviews and numerous guidelines from professional societies have explored the role of diet in AD.¹⁻¹⁰ The literature focuses on dietary supplementation, dietary exclusion, food allergy, maternal diet, and breastfeeding.

Dietary supplementation

A 2012 Cochrane review analyzed the evidence for dietary supplements as treatments for AD.¹

Abbreviations used:

AD:	atopic dermatitis
AK:	actinic keratoses
BCC:	basal cell carcinoma
BO:	borage oil
EPO:	evening primrose oil
GI:	glycemic index
GL:	glycemic load
NMSC:	nonmelanoma skin cancer
RCT:	randomized controlled trial
SCC:	squamous cell carcinoma
UV:	ultraviolet

Eleven randomized, controlled trials (RCTs) with 596 participants were included in the analysis, which addressed fish oil, zinc sulphate, selenium, vitamin D, vitamin E, pyridoxine, sea buckthorn seed oil, hempseed oil, sunflower oil, and docosahexaenoic acid. The reviewed studies were of poor quality and were too small to provide conclusive evidence for the benefit of dietary supplements in AD.¹

Vitamin D

Recent interventional studies investigated the impact of vitamin D supplementation on patients with AD. In 1 RCT, supplementation with 1600 IU daily for 2 months significantly improved Scoring Atopic Dermatitis (SCORAD) and 3-item severity scores compared to placebo.¹¹ Similarly, in a cross-sectional study, supplementation with 2000 IU daily for 3 months in patients with low serum vitamin D levels significantly improved SCORAD.¹² Conversely, in another RCT, supplementation with

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4000 IU daily for 2 months did not significantly impact the Eczema Area and Severity Index.¹³

Primrose and borage oils

Evening primrose oil (EPO) and borage oil (BO) are sources of gamma-linolenic acid, which is an antiinflammatory fatty acid that is thought to be deficient in patients with AD.³ A 2013 Cochrane review analyzed 27 studies with 1596 participants that investigated the oral intake of EPO or BO as treatment for AD. Taken together, there was no significant improvement in AD after short-term EPO or BO supplementation.³

Prebiotics and probiotics

The composition of intestinal bacteria is postulated to impact food sensitization in the gastrointestinal tract and AD pathogenesis. Prebiotics and probiotics alter intestinal microflora and reduce intestinal inflammation. Prebiotics are nondigestible food components, commonly oligosaccharides, and probiotics are live microorganisms.⁴⁻⁶ A 2013 Cochrane review that analyzed 4 studies including 1428 infants revealed a significant risk reduction for AD after prebiotic supplementation in infants.⁴ Cochrane reviews of probiotics yielded conflicting results.^{5,6} One review of 12 RCTs with 781 children found no significant difference in AD symptoms or severity after probiotic supplementation.⁶ The other included 6 studies with 2080 infants and identified a significant reduction in AD with probiotic supplementation in high-risk infants.⁵

Additional support for the protective role of probiotics is derived from 2 metaanalyses of maternal supplementation during pregnancy. A 2012 metaanalysis of 7 RCTs revealed a significant risk reduction of AD in 2- to 7-year-old children after prenatal lactobacilli administration.¹⁴ These findings were supported by a metaanalysis of 16 RCTs that found that prenatal followed by postnatal probiotic supplementation was protective for AD in both normal- and high-risk infants.¹⁵

Dietary exclusion and food allergy

Patients frequently report food as an exacerbating factor in AD and eliminate foods that they presume to be responsible. While immunoglobulin E (IgE)-mediated food allergies are reported in up to 40% of children with moderate AD, the contribution of these allergies to AD is questionable.¹⁶

A 2008 Cochrane review assessed dietary exclusions for the treatment of AD.² Data from 9 RCTs were reviewed: 6 studies of egg and milk exclusion, 1 study of few foods diet, and 2 studies of

elemental diet. There was no significant benefit of these diets for unselected patients with AD.² Conversely, an egg-free diet improved AD extent and severity in patients with positive egg-specific serum IgE.² The observed lack of benefit from exclusion diets in unselected patients may be related to a lack of allergy to the eliminated food in these patients.²

Two professional societies' guidelines make recommendations for the diagnosis and management of food allergy in AD patients.^{9,10} Diagnosis of an IgE-mediated food allergy relies on a combination of medical history, skin prick test, serum IgE testing, and oral food challenges.^{9,10,16} History, skin prick test, and allergen-specific serum IgE are not diagnostic because of their limited positive predictive value for clinical allergy.^{9,10,16-19} The diagnostic criterion standard is a double-blind, placebo-controlled food challenge, which is often impractical in clinical practice, and is appropriately replaced by a single-blind or open food challenge.^{9,10} A challenge is preceded by the elimination of suspected foods for 2 to 8 weeks and is administered in a supervised medical setting to enable treatment of hypersensitivity reactions.⁹ If the challenge does not elicit symptoms, an allergy to that food allergy is not present. A food allergy is confirmed if the challenge elicits symptoms that correlate with medical history, blood testing, and skin prick results.⁹

For patients with AD and a proven food allergy, elimination diets are appropriate and may decrease the severity of AD.^{9,10,16} Nutritionist consultation is indicated to avoid nutritional deficiencies and growth restriction.²⁰ In addition, because food allergies often spontaneously resolve, patients should be reassessed regularly to avoid unnecessary elimination.²¹ For patients without a proven food allergy, elimination diets should not be pursued to manage AD, because there is no evidence to suggest that this approach is helpful. In addition, these diets may cause nutritional deficiencies, growth deficits, and anaphylaxis on reexposure to previously tolerated foods.^{2,9,10,16,20,21}

Maternal diet and breastfeeding

A 2012 Cochrane review analyzing 5 RCTs with 952 participants found no significant protective effect of an antigen avoidance diet during pregnancy, lactation, or both for prevention of AD in infants up to 18 months of age.⁷ In addition, maternal antigen avoidance during pregnancy was associated with a decreased mean gestational weight gain and birth weight and increased risk of preterm birth.⁷ In 1 crossover study of 17 lactating women,

however, antigen avoidance was associated with a nonsignificant decrease in infant AD severity.⁷

In 2008, the American Academy of Pediatrics summarized the evidence for maternal and infant nutrition in the context of AD.⁸ Akin to the Cochrane review, they reported that restriction of maternal diet during pregnancy and lactation does not affect subsequent AD development. Exclusive breastfeeding for 4 months in high-risk infants was reported to be protective against AD.⁸ A metaanalysis of 18 prospective studies and the German Infant Nutritional Intervention studies found decreased AD incidence in high-risk infants who were breastfed compared to those fed cow's milk formula.²²⁻²⁴ This protective effect also applied to hydrolyzed formula.^{8,25} Conversely, no significant effect of exclusive breastfeeding on AD was observed for infants in the general population.²²⁻²⁷

Conclusions

There is insufficient evidence to suggest a benefit from supplementation with vitamin D, EPO, BO, fish oil, zinc sulphate, selenium, vitamin E, pyridoxine, sea buckthorn seed oil, hempseed oil, sunflower oil, and docosahexaenoic acid for AD. Evidence suggests that prebiotic supplementation in infants and prenatal followed by postnatal probiotic supplementation decrease the risk of AD. Elimination diets are only appropriate for patients who have a food allergy that is proven by oral food challenge. Maternal allergen avoidance diets during pregnancy or lactation do not prevent AD. Exclusive breastfeeding for 4 months or breastfeeding supplemented with hydrolyzed formula is protective against AD in high-risk infants. For infants at normal risk, breastfeeding does not affect the incidence of AD. Table I summarizes the recommendations along with providing the associated level of evidence.

ACNE

Key points

- **Multiple randomized controlled trials with biochemical and histopathologic evidence support the benefit of a low glycemic index/load diet for acne patients**
- **While observational studies suggest that frequent milk consumption imparts a higher risk of acne, randomized controlled trials are necessary before dietary recommendations can be made**

Many patients believe that diet contributes to acne.²⁸⁻³³ The relationship between diet and acne has emerged as a hot topic, with >10 reviews being devoted to the subject in the past 10 years.³⁴⁻⁴⁶

The literature addresses many foods, including fatty acids, chocolate, sugar, probiotics, and multivitamins, but only the 2 most commonly addressed—glycemic index/load and milk—will be discussed here.

Glycemic index/glycemic load

The diets of Kitavan Islanders of Papua New Guinea and the Ache hunter-gatherers of Paraguay are comprised of minimally processed plant and animal foods and devoid of typical Western carbohydrates.⁴⁷ Acne is absent among these populations, suggesting that a low glycemic load diet and subsequent lack of hyperinsulinemia with its associated endocrine cascade may be responsible.⁴⁷

Glycemic index (GI) is a numeric system that measures the rise in blood glucose triggered by a carbohydrate. Glycemic load (GL) ranks carbohydrate content based on GI and portion size.⁴⁸ The dermatocrinologic mechanism that underlies the link between dietary GI/GL and acne has been well described.^{39,44,48,49} Briefly, a high GI/GL diet leads to hyperinsulinemia, which initiates a signaling cascade resulting in increased insulin and insulin-like growth factor 1 (IGF-1) activity and decreased IGF-binding protein 3 (IGFBP-3) activity. Decreased IGFBP-3 effectively increases the bioavailability of IGF-1, compounding its direct activation. IGF-1 is known to stimulate key factors of acne pathogenesis, including keratinocyte proliferation, sebocyte proliferation, and lipogenesis.^{39,44,48,49} Both insulin and IGF-1 increase gonadal and adrenal androgen synthesis, decrease the hepatic synthesis of sex hormone-binding globulin (SHBG), and disinhibit androgen receptors, thereby directly activating and increasing the bioavailability of androgens. Androgens increase sebum production and contribute to acne pathogenesis.⁴⁸⁻⁵¹ Finally, IGFBP-3 is a potent proapoptotic factor in keratinocytes and corneocytes.⁴⁴

Smith et al⁵²⁻⁵⁵ published 4 interventional studies investigating the effect of a low GI/GL diet compared to a high GI/GL diet on acne. In 2 RCTs, low GI/GL groups had a significant decrease in acne counts and free androgen index and a significant increase in insulin sensitivity and IGFBP compared to high GI/GL groups.^{52,53} Both studies, however, were limited by the inability to isolate the effect of low GI/GL diet from weight loss. A subsequent study found no difference in sebum outflow, but an increased ratio of saturated to monounsaturated fatty acids in skin surface triglycerides in the low GI/GL group.⁵⁴ The change in skin surface triglycerides correlated with total lesion counts, suggesting that

Table I. Dietary modifications for patients with atopic dermatitis with recommendations and the associated level of evidence

Dietary modification	Recommendation	Level of evidence
Supplementation with		
Vitamin D	Insufficient data for conclusive recommendation	IB
Fish oil	Insufficient data for conclusive recommendation	IA
Zinc sulphate	Insufficient data for conclusive recommendation	IA
Selenium	Insufficient data for conclusive recommendation	IA
Vitamin E	Insufficient data for conclusive recommendation	IA
Pyridoxine	Insufficient data for conclusive recommendation	IA
Sea buckthorn seed oil	Insufficient data for conclusive recommendation	IA
Hempseed oil	Insufficient data for conclusive recommendation	IA
Sunflower oil	Insufficient data for conclusive recommendation	IA
Docosahexaenoic acid	Insufficient data for conclusive recommendation	IA
Evening primrose oil	No	IA
Borage oil	No	IA
Prebiotics	Yes, in infants	IA
Probiotics	Yes, prenatally and postnatally	IA
Elimination diets	Only for immunoglobulin E-mediated food allergy proven by observed food challenge	IA
Maternal allergen avoidance		
During pregnancy	No	IA
During lactation	No	IA
Exclusive breastfeeding	Yes, for at least 4 months in high-risk infants	IB
Hydrolyzed formula	Yes, in high-risk infants	IB

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

low GI/GL affects acne in part through sebaceous lipogenesis.⁵⁴ Finally, in a small, nonrandomized study, the low GI/GL group had a significant increase in insulin sensitivity and IGFBP-3, while the high GI/GL group had a significant increase in free androgen index and decrease in SHBG.⁵⁵ This series of interventional studies provides compelling evidence that a low GI/GL diet improves acne. Weight loss, however, is a confounding factor.

A recent RCT supported the findings of Smith et al⁵²⁻⁵⁵ and provided histopathologic support for the benefits of a low GI/GL diet on acne.⁵⁶ Low GI/GL diet led to a significant decrease in acne counts. Histopathologic examination revealed reduced sebaceous gland size and decreased expression of sterol regulatory element binding protein-1, a regulator of lipid synthesis, and interleukin-8, an inflammatory cytokine, with a low GI/GL diet.⁵⁶

Observational studies have also shown an association between glycemic load and acne. A case control study revealed a significantly higher dietary GL in acne patients compared to healthy controls, even with multivariate analysis accounting for body mass index.⁵⁷ Among 2258 patients

consuming the South Beach Diet, which emphasizes low GI foods,³⁷ 86.7% reported improved acne with diet and 91%⁵⁶ reported the ability to decrease dose or number of acne medications.⁵⁸ A community-based case control study found that patients consuming a Mediterranean diet, another low GI diet, were less likely to have acne.⁵⁹ Finally, a cross-sectional study identified higher dietary GI among participants with moderate to severe acne compared to those with no or mild acne.³³

Two studies do not support the association between GI/GL and acne. A nonrandomized trial that tested the effect of high compared to a low GI/GL diet in acne patients did not find significant differences in acne severity, insulin sensitivity, free androgen index, SHBG, IGF-1, or IGFBP-3 between groups.⁶⁰ A prospective cohort study also revealed no significant differences in GI/GL, serum glucose, insulin sensitivity, or IGF-1 in acne patients compared to controls.⁶¹

Milk

Akin to high GI carbohydrates, milk consumption significantly elevates insulin and IGF-1 levels and

Table II. Dietary modifications for patients with acne with recommendations and the associated level of evidence

Dietary modification	Recommendation	Level of evidence
Low glycemic index/load diet	Yes	IB
Milk restriction	Insufficient data for conclusive recommendation	III

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

decreases IGFBP-3 levels.⁴⁹ Milk also contains bovine IGF-1, which is identical to human IGF-1 and binds with the same affinity to its receptor.⁶² Increased insulin and IGF-1 signaling promote comedogenesis, sebaceous lipogenesis, follicular inflammation, and androgenic stimulation.⁶³ Milk also contains dihydrotestosterone precursors, including placenta-derived progesterone, 5 α -pregnanedione, 5 α -androstane, and numerous growth-related factors.⁶⁴

In a series of 3 studies, Abedamowo et al⁶⁵⁻⁶⁷ investigated the association between acne and milk consumption. In a retrospective cohort study of 47,355 women, using data from the Nurses' Health Study II, a self-reported history of physician-diagnosed severe acne was positively associated with the frequent consumption of total milk and skim milk.⁶⁵ Similarly, a prospective cohort study including 6094 girls found that self-reported acne was positively associated with total, whole, low fat, and skim milk consumption.⁶⁶ In a study of 4273 boys, self-reported acne was positively associated with skim milk intake only.⁶⁷ In addition, 2 case control studies and 1 cross-sectional study identified an increased risk of acne with more frequent milk consumption.^{33,57,68} Finally, a recent case series reported acne in 5 male patients that was precipitated by whey protein supplementation.⁶⁹ Whey protein comprises 20% of protein in cow's milk and is thought to be the insulinotropic component.⁴⁹ These patients experienced resolution of their acne after discontinuation of whey protein supplementation.⁶⁹

Conclusions

Currently, there are well described biochemical and physiologic mechanisms that explain the association of GI/GL and milk consumption with acne. There are multiple RCTs that have shown the benefit of a low GI/GL diet in treating acne, so this diet may be recommended to patients. While observational studies support the link between milk

and acne, RCTs are required before milk restriction diets can be recommended to acne patients. **Table II** summarizes recommendations along with the associated level of evidence.

NONMELANOMA SKIN CANCER

Key points

- A large randomized controlled trial found no significant effect of a low-fat diet on nonmelanoma skin cancer; therefore, a fat restricted diet should not be recommended for nonmelanoma skin cancer prevention
- Selenium supplementation may increase the risk of squamous cell carcinoma and total nonmelanoma skin cancer and should be avoided
- The effect of retinol and retinoid supplementation on nonmelanoma skin cancer varies based on risk factors, comorbidities, and cancer type

Fat

Animal studies suggest that dietary fat intake significantly influences the occurrence of NMSC.⁷⁰ Higher dietary fat decreases time latency between ultraviolet (UV) exposure and tumor onset and increases the number of tumors in mice.⁷¹

In a RCT of 115 patients with skin cancer history, the low-fat diet group developed fewer actinic keratoses (AKs) and NMSCs than controls.⁷¹⁻⁷³ One case control study found a direct relationship between dietary fat consumption and NMSC,⁷⁴ whereas another reported an inverse association.⁷⁵ Ten studies, including 1 very large RCT with 48,835 participants,⁷⁶ 5 cohort studies,⁷⁶⁻⁸¹ 4 case control studies,⁸²⁻⁸⁵ and 1 metaanalysis⁸⁶ did not identify a significant association between dietary fat and NMSC.

Vitamin A

Vitamin A and its derivatives, β -carotene and retinol, are important for epithelial cell proliferation

Table III. Dietary modifications for patients with nonmelanoma skin cancer with recommendations and the associated level of evidence

Dietary modification	Recommendation	Level of evidence
Low-fat diet	No	IB
Vitamin A supplementation	No	IB
β-carotene	Consider to decrease SCC in patients with moderate risk	IB
Retinol	Decrease NMSC in patients with xeroderma pigmentosum or renal transplant	IB
Synthetic retinoid (eg, isotretinoin, acitretin)		IIA and IB
Vitamin D supplementation	Insufficient data for conclusive recommendation	III
Vitamin E supplementation	Insufficient data for conclusive recommendation	III
Vitamin C supplementation	Insufficient data for conclusive recommendation	III
Selenium supplementation	Avoid due to increased risk of SCC and NMSC	IB

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥1 randomized controlled trial; level IIA evidence includes evidence from ≥1 controlled study without randomization; level IIB evidence includes evidence from ≥1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

NMSC, Nonmelanoma skin cancer; SCC, squamous cell carcinoma.

and differentiation, possess antioxidant properties, and protect against skin tumorigenesis in mice.⁸⁷⁻⁸⁹ As such, they are postulated to play a role in NMSC.

Human studies that investigate the association between vitamin A and NMSC yield conflicting results. One case control study revealed a lower mean serum level of β-carotene and vitamin A in NMSC cases than controls and a significant inverse relationship between dietary intake of β-carotene and NMSC.⁹⁰ Similarly, another case control study found that vitamin A consumption was associated with a reduced risk of basal cell carcinoma (BCC).⁹¹

In addition, a cohort study found lower mean serum retinol concentration in NMSC patients compared to controls.⁹² Two studies, however, reported a positive association between dietary vitamin A and BCC⁹³ and higher serum retinol levels in BCC cases compared to controls.⁹⁴ Multiple studies, including 6 case control^{83-85,95-97} and 8 cohort studies,^{74,77,79,81,98-101} were unable to identify a significant association between dietary intake of vitamin A derivatives, plasma or serum retinol levels, and NMSC.

Multiple interventional studies have evaluated the effect of retinol, isotretinoin, or β-carotene on NMSC incidence. Three RCTs found no significant difference in NMSC incidence between intervention and control groups after β-carotene supplementation.¹⁰²⁻¹⁰⁴ The study results for retinol and synthetic retinoids are more varied. One RCT revealed no significant difference in time to first NMSC or in total number of tumors in retinol-treated versus control high-risk patients.¹⁰⁵ Conversely, in patients with moderate risk, oral retinol supplementation

significantly decreased the hazard ratio for first squamous cell carcinoma (SCC), but did not affect BCC risk.¹⁰⁶ Similarly, in a RCT, 10 mg of isotretinoin daily did not affect BCC development.¹⁰⁷ Smaller studies of isotretinoin in patients with xeroderma pigmentosum^{108,109} and acitretin in renal transplant patients¹¹⁰ identified statistically significant reductions in NMSC incidence in treatment groups. These studies suggest that the impact of retinol and synthetic retinoids on NMSC may be affected by individual patient risk factors and comorbidities.

Vitamin D

Vitamin D is obtained exogenously through foods and endogenously through UV-induced calcitriol synthesis. In vitro studies in BCC¹¹¹ and SCC¹¹²⁻¹¹⁴ cell lines reveal differential expression and downstream effects of key components of the vitamin D system. Loss of the vitamin D receptor enhances susceptibility to UV-induced tumorigenesis in a mice.¹¹⁵ Vitamin D inhibits the hedgehog signaling pathway and upregulates nucleotide excision repair enzymes, potentially protecting against NMSC.^{116,117}

Despite evidence from animal and in vitro studies, human studies are conflicting. One case control study found an inverse relationship between vitamin D level and risk of NMSC.¹¹⁸ Conversely, 3 studies identified a significant positive association between plasma vitamin D levels and NMSC risk.¹¹⁹⁻¹²¹ Sun exposure may confound these results, because UV radiation simultaneously increases serum vitamin D levels and promotes DNA mutations that are key in the development of skin cancer. Three studies found

no association between dietary vitamin D and risk of BCC.^{74,77,85}

Vitamin E

Topical application of α -tocopherol, the most frequent naturally occurring form of vitamin E, inhibits ultraviolet B light (UVB)-induced DNA damage and carcinogenesis in mice.¹²²⁻¹²⁴ Human trials, however, yield conflicting data. Three case control studies reported a protective effect of vitamin E on NMSC development.^{85,91,125} Decreased plasma levels of α -tocopherol were found in patients with AK and BCC compared to controls.¹²⁵ Inverse associations between vitamin E dietary intake⁸⁵ and supplementation⁹¹ and subsequent BCC development were observed. Conversely, 2 cohort studies found a positive association between dietary and supplemental vitamin E and BCC development,^{93,99} while others were unable to identify an association between vitamin E supplementation or serum levels and subsequent NMSC.^{74,77,81,84,94-96,98,101} In addition, a double-blind, placebo-controlled study did not find a clinical or histologic difference in response to UVB after 6 months of daily oral α -tocopherol (400 IU) supplementation.¹²⁶

Vitamin C

In vitro studies of human keratinocyte cell lines show that ascorbic acid, which is a stable form of vitamin C, decreases UVB-induced cytotoxicity as a free radical scavenger and a potentiator of the antioxidative activity of α -tocopherol.^{127,128} Vitamin C administration significantly inhibits UV-induced DNA, RNA, and protein synthesis in BCC and SCC cell lines in mice and rats.¹²⁹⁻¹³¹ The photoprotective properties of topical vitamin C have been shown in porcine skin.¹³²

In humans, studies of vitamin C and NMSC are inconsistent. Inverse relationships between the consumption of vitamin C-containing foods,⁹⁰ vitamin C supplements,⁹¹ and plasma levels of ascorbic acid¹²⁵ with NMSC were identified in 3 case control studies. Conflicting results were obtained in 2 cohort studies that identified a positive association between BCC and the intake of vitamin C-rich food or supplements.^{93,99} In addition, 3 case control studies⁸³⁻⁸⁵ and 5 cohort studies^{74,77,79,81,98} failed to identify a significant association between vitamin C and NMSC.

Selenium

Selenium protects against UVB-induced cytotoxicity in human keratinocytes and carcinogenesis in mice.¹³³⁻¹³⁵ Studies have found a potentially protective role of selenium for NMSC. In a case

control study, the mean plasma selenium level was significantly lower amongst NMSC cases than controls.¹³⁶ Similarly, a cohort study found an inverse relationship between serum selenium concentration and subsequent NMSC.¹⁰⁰ Finally, in a study of 8 women treated with topical L-selenomethionine for 2 weeks, a significant increase in minimal erythema dose after UV irradiation was observed, suggesting a possibly photoprotective effect of topical selenium.¹³⁷

The only RCT that has investigated the impact of oral selenium supplementation on NMSC found no significant association with risk of BCC, but, interestingly, elevated risks of SCC and total NMSC.¹³⁸ Other studies found no significant association between dietary^{84,85} or plasma selenium^{94,95} and NMSC.

Conclusions

In conclusion, despite laboratory evidence suggesting a link between dietary factors and NMSC, human studies have been contradictory and inconclusive. Observational studies provide conflicting results and often do not reveal a significant association between dietary factors and NMSC. A large RCT of patients who were following a low-fat diet ($n = 48,835$) found no significant difference in NMSC; therefore, a fat-restricted diet should not be recommended for NMSC prevention. Based on a RCT, selenium supplementation may increase the risk of SCC and total NMSC and should be avoided. Interventional studies suggest that the effect of retinol and retinoid supplementation on NMSC varies based on risk factors, comorbidities, and skin cancer type. Table III summarizes the recommendations along with the associated level of evidence.

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Diet in dermatology

Part II. Melanoma, chronic urticaria, and psoriasis

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Learning objectives

After completing this learning activity, participants should be able to describe the relationship between diet and the following conditions: atopic dermatitis, skin cancer, and vitamin D deficiency.

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The roles of dietary factors in aggravating, preventing, or treating skin diseases are common questions encountered in dermatology practice. Part II of this two-part series reviews dietary modifications that can potentially be utilized in the management of melanoma, chronic urticaria, and psoriasis patients. Specifically, we examine the effect of alcohol consumption and supplementation with vitamins D and E, polyunsaturated fatty acids, selenium, green tea, resveratrol, and lycopene on melanoma risk. The relationships between chronic urticaria symptoms and dietary pseudoallergens, gluten, and vitamin D are analyzed. We explore weight loss, reduced alcohol consumption, and gluten avoidance as means of reducing psoriasis-associated morbidity, as well as the possible utility of supplementation with polyunsaturated fatty acids, folic acid, vitamin D, and antioxidants. With proper knowledge of the role of diet in these cutaneous disease processes, dermatologists can better answer patient inquiries and consider implementation of dietary modifications as adjuncts to other treatments and preventative measures. (J Am Acad Dermatol 2014;71:1053.e1-16.)

Key words: chronic urticaria; diet; melanoma; nutrition; psoriasis.

The role of dietary factors in dermatologic disease is a frequent source of patient inquiry and physician uncertainty. In part I of this continuing medical education article, we analyzed the effects of dietary modifications on atopic dermatitis, acne, and nonmelanoma skin cancer pathogenesis, risk modification, and treatment. In part II, we review the dietary factors that can potentially be used in the management of patients with melanoma, chronic urticaria, and psoriasis. **Tables I through IV** summarize the key dietary factors relating to melanoma, chronic urticaria, and psoriasis.

MELANOMA

Key points

- **Insufficient evidence exists to recommend supplementation with polyunsaturated fats, vitamins D and E, selenium, green tea, resveratrol, and lycopene to prevent the development or progression of melanoma in the general population**
- **Decreased alcohol intake and vitamin D supplementation may lower melanoma risk in high-risk patients**

Polyunsaturated fatty acids

Polyunsaturated omega-3 fatty acids (PUFAs) are antiinflammatory molecules that protect against ultraviolet (UV) damage.^{1,2} PUFA supplementation decreases skin sensitivity to UV irradiation and cutaneous expression of p53 in animal and human studies.³⁻⁵ Additionally, in animal and in vitro studies, PUFAs were shown to increase apoptosis,^{6,7}

Abbreviations used:

DLQI:	Dermatology Life Quality Index
EGCG:	epigallocatechin-3-gallate
IgE:	immunoglobulin E
PASI:	Psoriasis Area and Severity Index
PUFA:	polyunsaturated omega-3 fatty acid
RCT:	randomized, controlled trial
UV:	ultraviolet

promote cell cycle arrest,⁷ and decrease tumor growth.^{3,8,9} PUFAs can inhibit metastatic melanoma,¹⁰⁻¹² and when used as an adjunct to surgery they promote recurrence-free survival.¹² Some animal studies of PUFA supplementation found increased tumor growth and immunosuppression.¹³⁻¹⁵ These conflicting results of in vitro and animal studies do not elucidate a protective role of PUFAs against melanomagenesis.

Clinical data are also conflicting. Three studies, including 2 case control trials and 1 prospective cohort study, reported an increased risk of melanoma in patients with higher dietary PUFA intake.¹⁶⁻¹⁸ In contrast, the incidence of melanoma is low in populations with PUFA-rich diets, including Inuits¹⁹ and cohorts in both Italy²⁰ and Australia.²¹

Alcohol

The role of alcohol consumption in melanomagenesis is complex and involves the interplay of biologic, behavioral, and epidemiologic factors. From a cellular standpoint, ethanol induces DNA damage, promotes the production of reactive

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Table I. Diet and melanoma: Proposed mechanism of action and human studies with the associated level of evidence

Dietary modification	Proposed mechanism of action	Human randomized controlled trials (yes/no) and level of evidence
Polyunsaturated fatty acid supplementation	Antiinflammatory; UV photoprotective; induce apoptosis; decrease tumor growth and metastatic disease; and promote recurrence-free survival	No; III
Reduced alcohol consumption	Decreased UV-induced and DNA damage; diminished immune function; and decreased prostaglandin and melanocyte-stimulating hormone production	No; III
Oral vitamin D supplementation	Antiproliferative; proapoptotic; pro-cell differentiation; and decreased metastatic potential	Yes; IB
Vitamin E supplementation	Antioxidant; anticarcinogenic; UV photoprotective; and immunomodulating	Yes; IB
Selenium supplementation	Relieves UV-induced depletion of glutathione peroxidase; proapoptotic; and induces cell cycle arrest	No; III
Supplementation with green tea polyphenols	Antiinflammatory; immunomodulating; anticarcinogenic; proapoptotic; and UV photoprotective	No; III
Supplementation with resveratrol	UV photoprotective, antioxidant; antiinflammatory; anticarcinogenic; increased cell survival; proapoptotic; induces cell cycle arrest; and inhibits metastatic disease	No; III
Supplementation with lycopene	UV photoprotective; antioxidant; and decreased metastatic disease	No; III

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

UV, Ultraviolet light.

oxygen species, acts as a photosensitizer, and alters cellular metabolism.²²⁻²⁶ Hormonal effects of ethanol include promoting prostaglandin synthesis²³ and the secretion of melanocyte-stimulating hormone.²⁷ Finally, alcohol consumption alters immune function²⁸⁻³¹ and increases the metastatic potential and growth of melanoma cells.^{32,33}

Several large, population-level studies have found a positive association between alcohol consumption and melanoma risk.^{21,22,34-39} In fact, a recent systematic review reported a 20% increase in melanoma risk in patients who regularly consumed alcohol.⁴⁰ A potential confounding factor is increased high-risk behaviors in alcohol users, including sunburns.⁴¹ Three smaller case control studies, however, found no association between alcohol consumption and melanoma risk,⁴²⁻⁴⁴ and 1 population-level study reported decreased melanoma risk among Swedish women who were also alcoholics.⁴⁵

Vitamin D

Vitamin D and its analogues have antiproliferative, proapoptotic, prodifferentiation, and antiinvasive properties in human melanoma cell lines.⁴⁶⁻⁵⁰

In addition, polymorphisms of the vitamin D receptor gene may impact melanoma risk.⁵¹⁻⁵⁴ The relationship between serum vitamin D levels, dietary vitamin D supplementation, and melanoma risk, however, still remains largely uncertain.⁵⁵

Observational studies investigating vitamin D status and melanoma risk provide conflicting results. Two large, prospective cohort studies^{56,57} reported an increased melanoma incidence in patients with higher serum vitamin D levels. Another nested case control study found no association between serum vitamin D levels and melanoma risk.⁵⁸ In addition, 1 case control and another cohort study found no association between dietary vitamin D and melanoma risk,^{59,60} while others reported an inverse relationship.^{22,61} In addition, multiple case control studies have reported inverse associations between vitamin D levels and poorer melanoma prognosis—namely, an increased Breslow thickness and more advanced stage.⁶²⁻⁶⁵ Earlier metastatic disease occurred in patients with low serum vitamin D levels,⁶³ whereas higher vitamin D levels were independently protective against melanoma relapse and death.⁶²

Table II. Diet and chronic urticaria: Allowed and prohibited food items in a pseudoallergen-free diet

Food item	Allowed	Prohibited
Breads and other carbohydrates	Breads without preservatives, semolina, millet, potatoes (but not french fries), rice, durum, egg-free wheat noodles, and rice waffles	All others
Fats	Butter and vegetable oils	All others
Milk products	Fresh milk, fresh cream, curd, natural yogurt, and cream cheese	All others
Meats and seafood	Fresh meat, fresh unseasoned ground meat, and self-made cold meat	All processed meats, eggs, fish, and crustaceans
Vegetables	All others	Artichokes, peas, mushrooms, rhubarb, spinach, tomatoes and tomato sauces, olives, and peppers
Fruits	None	All fruits, including dried fruits and other fruit products
Spices	Salt, sugar, chives, and onions	Garlic and all other spices and herbs
Sweets	None	All sweets, including those with artificial sweeteners
Beverages	Milk, mineral water, coffee, and black tea	All other beverages, including herbal teas and alcohol

Adapted from Reese et al.¹³²**Table III.** Diet and chronic urticaria: Proposed mechanism of action and human studies with the associated level of evidence

Dietary modification	Proposed mechanism of action	Human randomized controlled trials (yes/no) and level of evidence
Pseudoallergen-free diet	Decreased need for medications; improved DLQI; and antiinflammatory	Yes; IB
Gluten-free diet	Antiinflammatory; decreased production of anti-IgE receptor antibodies	No; III
Vitamin D supplementation	Improves vitamin D deficiency present in some patients with chronic urticaria	Yes; IB

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

DLQI, Dermatology Life Quality Index; IgE, immunoglobulin E.

A randomized, controlled trial (RCT) with 36,282 participants found no significant difference in incident melanoma rates in the intervention group (calcium plus 400 IU vitamin D₃ daily) compared to placebo.⁶⁶ Interestingly, in high-risk patients with a history of nonmelanoma skin cancer, supplementation resulted in a significantly lower melanoma risk, suggesting a potential role for vitamin D supplementation in this population.⁶⁶

Vitamin E

Vitamin E possesses antioxidant, anticarcinogenic, photoprotective, and immunomodulating properties.⁶⁷⁻⁷⁴ Cell and animal studies have shown that vitamin E is a free radical scavenger, inhibits cell proliferation and angiogenesis, promotes apoptosis, suppresses growth and invasion of tumor cells,

reverses UV-induced damage, and increases sensitization to chemotherapeutic drugs.^{71,73,75-78}

Despite this experimental evidence, epidemiologic studies have yielded inconsistent results. Multiple studies found no association between vitamin E and melanoma risk.^{39,79,80} Other studies^{21,81,82} have suggested inverse correlations between melanoma incidence and serum and diet vitamin E levels, supporting a protective role. However, a RCT of 9541 patients reported no differences in melanoma incidence in patients receiving long-term vitamin E supplementation (400 IU/day) compared to controls.⁸³ The safety of vitamin E supplementation is also unclear, because increased all-cause mortality was found in patients receiving high-dose (≥ 400 IU/day) vitamin E.⁸⁴

Table IV. Diet and psoriasis: Proposed mechanism of action of dietary modifications and human studies with the associated level of evidence

Dietary modification	Proposed mechanism of action	Human randomized controlled trials (yes/no) and level of evidence
Weight loss	Diminished proinflammatory state; improved PASI and DLQI; and increased efficacy of some medications	Yes; IB
Reduced alcohol consumption	Decreased medication toxicity and increased efficacy and decreased anxiety, depression, cardiovascular disease, solid tumor risk, and overall mortality	No; III
Polyunsaturated fatty acid supplementation	Antiinflammatory by decreasing levels of leukotriene B ₄ and decreased medication toxicity	Yes; IB
Gluten-free diet	Decreased production of tissue transglutaminase and other celiac disease-specific antibodies	No; IIB
Folic acid supplementation	B vitamin essential for cell growth, metabolism, and DNA function; antithrombotic and cardioprotective by lowering homocysteine levels; and decreases methotrexate toxicity	Yes; IA
Oral vitamin D supplementation	Adjunct to acitretin and protective against cardiovascular disease and metabolic syndrome	Yes; IB
Supplementation with selenium and other antioxidants	Antioxidant; essential for the functioning of glutathione peroxidase; and improve PASI and DLQI	Yes; IB

Levels of evidence are based on the *Journal of the American Academy of Dermatology* guidelines. Level IA evidence includes evidence from metaanalysis of randomized controlled trials; level IB evidence includes evidence from ≥ 1 randomized controlled trial; level IIA evidence includes evidence from ≥ 1 controlled study without randomization; level IIB evidence includes evidence from ≥ 1 other type of experimental study; level III evidence includes evidence from nonexperimental descriptive studies, such as comparative studies, correlation studies, and case control studies; and level IV evidence includes evidence from expert committee reports or opinions or clinical experience of respected authorities, or both.

DLQI, Dermatology Life Quality Index; PASI, Psoriasis Area and Severity Index.

Selenium

Selenium is a trace element and antioxidant that relieves the UV-induced depletion of glutathione peroxidase⁸⁵ and appears to induce dose-dependent apoptosis and cell cycle arrest in human melanoma cell lines.⁸⁵⁻⁸⁷ In animal studies, oral selenium supplementation resulted in decreased melanoma tumor growth⁸⁵ and reduced pulmonary^{88,89} and brain⁹⁰ metastases in mice.

Human studies, however, are conflicting. In 1 case control study, increased environmental exposure to selenium yielded a nearly 4-fold greater melanoma incidence than in unexposed controls.⁹¹ Other studies found no significant relationship between selenium levels and melanoma risk.⁹²⁻⁹⁵ Conversely, metastatic melanoma patients in a case control study were found to have significantly lower selenium levels than controls.⁹⁶

Green tea polyphenols

Polyphenols found in green tea, including epigallocatechin-3-gallate (EGCG), possess antioxidant, antiinflammatory, immunomodulatory, anticarcinogenic, proapoptotic, and photoprotective properties.⁹⁷⁻¹⁰¹ EGCG inhibits melanoma cell invasion and migration.¹⁰² In addition, green tea supplementation

during interferon therapy decreases melanoma cell growth in mice, suggesting its possible use as a treatment adjunct.¹⁰³ Despite these promising cell and animal studies, a prospective cohort study was unable to find a significant association between tea consumption and melanoma incidence.¹⁰⁴

Resveratrol

Resveratrol is a naturally occurring polyphenolic compound found in grapes, red wine, some berries, and peanuts.^{105,106} Resveratrol and its chemical analogues have photoprotective, antioxidant, anti-inflammatory, and anticarcinogenic capabilities. The introduction of resveratrol in cell cultures and topical application in human skin resulted in increased cell survival, decreased production of reactive oxygen species, and diminished clinical erythema after UV irradiation.¹⁰⁷⁻¹⁰⁹ Resveratrol induces the apoptosis of human melanoma cells and promotes cell cycle arrest.¹¹⁰⁻¹¹⁴ In addition, resveratrol may have a role in metastatic disease, because it possesses antiangiogenic properties¹¹⁵ and inhibits hepatic and pulmonary metastases.^{116,117} Resveratrol can be used as an adjunct to chemotherapy,^{118,119} radiation,¹²⁰ and interleukin-2¹¹⁷ by sensitizing melanoma cells to these treatments and preventing

toxic endothelial cell injury. While RCTs and population-level human trials are still lacking, 1 observational study reported decreased skin toxicity in breast cancer patients being treated with external beam radiation after supplementation with a mixture of vitamins and antioxidants, including resveratrol.¹²¹

Lycopene

Lycopene is a carotenoid that is found in red fruits and vegetables.¹²² It is a potent antioxidant and free radical scavenger¹²² that protects against UV photodamage. In animal and human cutaneous models, topical application of lycopene before UV irradiation decreases the inflammatory response, diminishes the generation of matrix metalloproteinases, increases the mean erythema dose, and preserves DNA integrity and normal cell proliferation.^{123,124} Similarly, oral lycopene supplementation decreases toxicity from external beam radiation in patients with breast cancer.¹²¹ Finally, lycopene inhibits platelet-derived growth factor-BB and melanoma-induced fibroblast migration, which are known to facilitate metastatic disease.¹²⁵

From an epidemiologic perspective, the association between lycopene and melanoma risk is unclear. Three case control studies found no significant association between serum lycopene levels and risk of subsequent melanoma.^{39,80,95} When dietary lycopene intake was stratified into quintiles, however, 1 case control study found that patients in the highest quintile had a significantly lower melanoma risk.²²

Conclusions

The role of diet on melanoma chemoprevention remains largely controversial. There is suggestive yet inadequate evidence—largely from in vitro and animal studies—supporting decreased alcohol consumption and supplementation with PUFAs, vitamin D, selenium, green tea, resveratrol, and lycopene as means to reduce melanoma risk. Observational studies, however, have produced conflicting results and are often unable to find an association between these dietary factors and melanoma risk in humans. In addition, interventional RCTs investigating the impact of supplementation on melanoma have not yet been conducted for PUFAs, selenium, green tea, resveratrol, or lycopene. Interventional studies suggest that vitamin E supplementation is of no value and vitamin D supplementation may be protective against melanoma in high-risk patients. Finally, the effect of alcohol consumption on melanoma risk is still unclear. Considering the general health benefits that

result from reduced alcohol consumption, melanoma patients and other high-risk individuals should be counseled regarding the potentially protective role of decreased alcohol intake on melanoma development. Green tea, resveratrol, and lycopene are generally considered to be safe and inexpensive. As such, they can be considered as possible additional protective methods, though efficacy remains to be convincingly proven.

CHRONIC URTICARIA

Key points

- **Interventional trials support the benefit of a pseudoallergen-free diet and vitamin D supplementation for patients with chronic urticaria**
- **Given its low cost and safety profile, a pseudoallergen-free diet can be recommended to a subset of chronic urticaria patients**
- **Before issuing a recommendation for vitamin D supplementation, appropriate dosage and treatment duration should be determined through randomized, controlled trials**
- **A gluten-free diet may ameliorate chronic urticaria symptoms in patients who have concomitant celiac disease; however, there are currently no randomized, controlled trials to support this recommendation**

Pseudoallergens

Pseudoallergens, including artificial preservatives, dyes, and aromatic compounds in processed and natural foods, are hypothesized to induce intolerance and hypersensitivity reactions with clinical manifestations mimicking those of immunoglobulin E (IgE)—mediated allergic diseases. Pseudoallergies are distinguished from traditional allergies because IgE antibodies against allergens are frequently absent, skin prick testing is often negative, and exposure to the provoking agents does not yield reproducible positive clinical symptoms.¹²⁶ Although the existence of pseudoallergens is not universally accepted and remains somewhat controversial, pseudoallergens are postulated to induce or aggravate chronic urticaria in a subset of patients.¹²⁶⁻¹³⁰ Pseudoallergen-induced urticaria may be related to increased gastroduodenal permeability¹³¹ or altered histamine metabolism.¹³²

Several studies, including 3 double-blind, placebo-controlled trials,¹³³⁻¹³⁵ found that pseudoallergen-free diets improved symptoms in a small subset of patients with chronic urticaria,

including those who were unresponsive to standard treatments.^{126,127,136-138} Conversely, a recent trial of 100 patients with chronic idiopathic urticaria found sensitivity to food and drug additives in <1% of patients, suggesting a limited utility of pseudoallergen elimination diets in the majority of chronic urticaria patients.¹³⁹ In 1 study, eliminating dietary pseudoallergens resulted in a decreased need for medications and improved quality of life.¹²⁶ In addition, the dietary elimination of pseudoallergens results in significantly lower urinary leukotriene E4, reflecting an antiinflammatory effect.¹⁴⁰ If a pseudoallergen-free diet results in clinical improvement, patients are then exposed to a pseudoallergen-rich “super meal.” If a positive reaction occurs, double-blind, placebo-controlled individual food challenges are performed in order to isolate specific triggers.¹³²

Gluten

Because some cases of urticaria are immune-mediated, it is not surprising that an association between chronic urticaria and celiac disease has been proposed.¹⁴¹⁻¹⁴⁵ Chronic urticaria may be a cutaneous manifestation of celiac disease.¹⁴⁶ Alternatively, increased mucosal permeability in celiac disease can facilitate the passage of antigens, provoking urticaria symptoms.¹⁴¹ In addition, the inflammatory response generated in celiac disease may trigger production of anti-IgE receptor antibodies that inappropriately activate mast cells; this pathogenic mechanism has been implicated in 35% to 40% of cases of chronic urticaria.^{147,148} In addition, there are several case reports and 1 small case control study that reported the resolution of urticaria in patients with concomitant celiac disease soon after initiating a gluten-free diet.^{141,142,144,145,149,150}

Vitamin D

Compared to unaffected controls, patients with chronic urticaria have significantly lower serum vitamin D levels.^{151,152} A retrospective case series reported decreased vitamin D levels (<32 ng/dL) in 90% of participants and complete clinical resolution of urticaria after vitamin D supplementation (50,000 IU/week) for 8 to 12 weeks in 70% of participants.¹⁵³ Similar improvements were described after vitamin D supplementation (2000 IU/day) for 2 months in a patient with chronic urticaria and vitamin D deficiency.¹⁵⁴ Finally, a RCT found that high-dose (4000 IU/day) vitamin D supplementation improves chronic urticaria regardless of baseline vitamin D status.¹⁵⁵

Conclusions

Interventional trials support the benefit of pseudoallergen-free diets and vitamin D supplementation for patients with chronic urticaria. Given its low cost and safety profile, a pseudoallergen-free diet can be recommended to chronic urticaria patients. Before issuing a recommendation for vitamin D supplementation, appropriate dosage and duration should be determined by additional RCTs. Finally, a gluten-free diet can be considered in patients who screen positive for celiac disease-related antibodies; however, there are currently no RCTs to support this recommendation.

PSORIASIS

Key points

- Weight loss and decreased alcohol consumption improve psoriasis symptoms and may increase the efficacy of some psoriasis medications
- Dietary supplementation with polyunsaturated fatty acids, folic acid, vitamin D, and antioxidants can be considered as adjuncts in the management of some psoriasis patients. Randomized, controlled trials have produced conflicting results, necessitating additional studies before definitive recommendations can be made
- A gluten-free diet may be efficacious in improving cutaneous symptoms in patients with psoriasis with celiac disease–related antibodies. Randomized, controlled trials, however, are still lacking at this time

Weight loss

Metabolic syndrome is more common among psoriasis patients.¹⁵⁶⁻¹⁵⁸ Specifically, increased adiposity, including obesity and weight gain, increases the risk of psoriasis.¹⁵⁹⁻¹⁶⁵ An obesity-induced proinflammatory state may exacerbate psoriasis symptoms,¹⁶⁶ and psoriasis itself may contribute to weight gain,^{167,168} partially because of social isolation, unhealthy dietary habits, and reduced physical activity.¹⁶⁵

In clinical studies, weight loss appears to significantly improve psoriasis symptoms. Diet and exercise reduce the Psoriasis Area and Severity Index (PASI) score in interventional patients compared to controls.¹⁶⁹ A low calorie diet and weight loss also resulted in improved PASI, Dermatology Life Quality Index (DLQI), and serum lipid levels.^{170,171} In addition, bariatric surgery–induced weight loss led to the clinical improvement of psoriasis and a decreased need for psoriasis medications.¹⁷²⁻¹⁷⁴

Weight loss may also improve the efficacy of some psoriasis medications. A study of obese patients with moderate to severe psoriasis treated with biologic agents found that PASI 75 or PASI 90 were more often achieved in patients who lost weight, even if they were previous nonresponders.¹⁷⁵ Increased clinical efficacy of cyclosporine following weight loss has also been reported.^{176,177}

Alcohol

The relationship between psoriasis and alcohol consumption is complex and multifactorial. Evidence suggests that alcohol triggers psoriasis and that alcohol abuse is more common among patients with psoriasis.¹⁷⁸⁻¹⁸² Alcohol abuse positively correlates with psoriasis severity¹⁸¹⁻¹⁸³ and reduced treatment efficacy.^{184,185} Hepatotoxicity associated with psoriasis medications occurs more frequently in patients who abuse alcohol.^{186,187} Psoriasis patients have a higher incidence of alcoholic liver disease,¹⁸² anxiety, depression,¹⁸¹ cardiovascular disease,¹⁸⁸ and solid tumor risk.¹⁸⁹ These trends may be caused, in part, by alcohol consumption. In fact, a large, 22-year prospective cohort study suggested that alcohol abuse was associated with significantly increased mortality rates in patients with moderate to severe psoriasis compared to controls.¹⁸³

PUFAs

Arachidonic acid, which is elevated in psoriatic lesions,¹⁹⁰ is converted into leukotriene B₄, a potent proinflammatory mediator.¹⁹¹ PUFAs, such as eicosapentaenoic acid and docosahexaenoic acid, are metabolized to leukotriene B₅, a considerably weaker inflammatory molecule.¹⁹² Increased levels of PUFAs are postulated to decrease inflammation and improve psoriasis symptoms.¹⁷⁸

Studies investigating the effect of fish or fish oil supplementation on psoriasis have produced inconsistent results. Several small, uncontrolled studies reported improvement of cutaneous lesions and psoriatic arthritis after oral supplementation with fatty fish or fish oil.¹⁹³⁻¹⁹⁶ Double-blind, placebo-controlled trials, however, have been conflicting.¹⁹⁷⁻²⁰⁰ A RCT with 45 participants observed no clinical difference in psoriasis symptoms after supplementation with very long chain n-3 fatty acids daily or corn oil daily.²⁰¹

Finally, dietary fish oil may decrease the side effects of psoriasis medications. Improvements in both retinoid-induced hyperlipidemia and hypertriglyceridemia and cyclosporine-induced nephrotoxicity have been reported after oral fish oil supplementation.²⁰²⁻²⁰⁴

Gluten

Celiac disease and psoriasis are reported to occur simultaneously.²⁰⁵⁻²⁰⁸ Observational studies, however, attribute this link to coincidence alone,²⁰⁹ while others discuss the meaning of celiac disease-related antibodies in psoriasis patients.^{210,211} For psoriasis patients with celiac-specific antibodies, a gluten-free diet improves psoriasis lesions.^{212,213} Interestingly, in a study of 28 psoriasis patients, tissue transglutaminase was overexpressed in the lesional dermis of patients with antibodies to gliadin. After 3 months of a gluten-free diet, clinical improvement was accompanied by decreased tissue transglutaminase expression.²¹²

Folic acid

An increased incidence of folic acid deficiency has been reported in psoriasis patients. This observed deficiency may be related to elevated homocysteine levels,^{214,215} decreased intestinal absorption caused by inflammation,²¹⁶⁻²¹⁸ and increased use by skin epidermal cells.²¹⁹⁻²²¹ Folate deficiency is also implicated in psoriasis severity. In a case control study, significantly elevated plasma homocysteine and significantly reduced plasma folate levels were found among patients with psoriasis compared to healthy controls.²¹⁵ Plasma homocysteine levels directly correlated with PASI, whereas folate levels were inversely related to PASI.^{215,222}

Folate supplementation has been postulated to have an antithrombotic and cardioprotective role in some psoriasis patients²²³; a recent review article, however, found insufficient evidence to support this claim.²²⁴ Folate supplementation may also be useful for psoriasis patients who have been treated with methotrexate. Four systematic reviews found diminished adverse side effects of methotrexate therapy, such as hepatotoxicity and gastrointestinal intolerance, after folate supplementation.^{186,225-227} Of note, a reduction in the efficacy of methotrexate with concurrent folate supplementation has also been reported.^{226,228,229}

Vitamin D

The utility of topical vitamin D in the treatment of psoriasis is well established, but the role of oral vitamin D supplementation remains unclear. A correlation between low serum vitamin D levels and increased severity of psoriasis has been suggested.²³⁰ Observational studies have shown the safety and efficacy of oral vitamin D supplementation in the treatment of psoriatic lesions²³⁰⁻²³⁴ and psoriatic arthritis.²³³ Oral vitamin D is also a useful adjunct to other medications, such as acitretin,²³⁵ may be used in the management of patients with

erythrodermic or pustular psoriasis,²³⁶ and can potentially be protective against some of the systemic manifestations of psoriasis, such as metabolic syndrome and cardiovascular disease.²³⁷ Of note, a recent randomized, placebo-controlled trial found no significant difference in improvement of skin lesions in patients treated with oral vitamin D compared to controls.²³⁸

Selenium and other antioxidants

Increased oxidative stress and circulating free radicals may contribute to the inflammatory state of psoriasis. Antioxidants, particularly selenium, vitamin E, and β-carotene, can offset this oxidative imbalance.²³⁹ Evidence supporting the amelioration of psoriasis symptoms after antioxidant use, however, is weak. Selenium supplementation has been studied most extensively. Selenium is essential for the normal functioning of glutathione peroxidase and may be found in low levels in patients with psoriasis, particularly those with extended disease duration.²⁴⁰⁻²⁴² A prospective study of psoriasis patients with normal baseline selenium levels failed to show improvement of clinical symptoms after supplementation with selenium-enriched yeast.²⁴³ Similarly, combined selenium and vitamin E supplementation in patients with moderate to severe plaque psoriasis and low serum selenium levels did not yield any noticeable change in cutaneous lesions despite achieving increased platelet glutathione peroxidase activity in 1 randomized, placebo-controlled trial.²⁴⁰ Combination antioxidant therapy with selenium, coenzyme Q10, and vitamin E, on the other hand, was associated with rapid clinical improvement and reduction of cell markers of oxidative stress.²⁴⁴ One randomized, double-blind, placebo-controlled trial also reported reduced PASI and improved DLQI after β-carotene supplementation.²⁴⁵

Conclusions

Dermatologists should encourage overweight and obese psoriasis patients to attempt weight loss and increased physical activity in order to improve psoriasis symptoms, comorbid metabolic syndrome, and medication efficacy. Given the prevalence of alcohol use among patients with psoriasis, screening for abuse is advised. The Alcohol Use Disorders Identification Test, Michigan Alcohol Screening test, and CAGE questionnaire may be used to identify psoriasis patients who suffer from alcohol abuse or dependence.¹⁷⁸ Screening should be considered for celiac disease, and implementation of a gluten-free diet may improve both conditions, if they are present simultaneously. Despite a few promising studies,

consistent evidence supporting PUFA, vitamin D, and antioxidant supplementation is currently lacking and additional studies are required before concrete recommendations can be made.

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